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A STUDY OF THE EFFECTS OF THE ADRENOCORTICOTROPIC HORMONE (ACTH) AND CORTISONE IN CERTAIN SELECTED DISEASES

—HATFIELD—

Thesis
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A STUDY OF THE EFFECTS OF THE ADRENOCORTICOTROPHIC HORMONE (ACTH) AND CORTISONE IN CERTAIN SELECTED DISEASES.

A DISSERTATION

SUBMITTED TO THE SCHOOL OF GRADUATE STUDIES

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OF MASTER OF SCIENCE

FACULTY OF ARTS AND SCIENCE

by

CLINTON BRUCE HATFIELD

EDMONTON, ALBERTA

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ERRATA

Acknowledgement line 4 "advise" to read "advice".

Table of Contents, Page 2, V11 (b) (2) "Metabolus" to read "Metabolism".

Page 34, line 26, "fasciculata" to read "glomerulosa".

Page 47, line 16,"suggested to read "suggests".

Page 50, line 14, (Fg.2) to read (Fig. 2).

Page 54, line 19,"stimulatory" to read "stimulating".

Page 89, line 8,"ocrtisone" to read "cortisone".

Page 99, line 9, delete "on".

Page139, line 21,"rate" to read "rats".

Appendix I, page i, line 25, "balance" to read "balanced".

Bibliography,Reference #217, delete "Hoffman, M. M., Browne, J. S. L." so as to read "Venning, E. H., Kazmin, V. E., and Bell,J. C."

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HISTORICAL INTRODUCTION

Prior to the middle of the sixteenth century the adrenal glands were unknown structures. They were first described by Bartholomaeus Eustachius in 1563 in his book "Opuscula Anatomica Gentus" under the title "De Glandulis Quae Renibus Incumbunt". Despite the clear exposition of Eustachius (1), it took more than three hundred years before any indication of their probable action was obtained.

During the middle of the nineteenth century advances were made in the anatomical study of the adrenals. Ecker (2) in 1846 first demonstrated the glandular nature of the adrenal cells, and concluded that these organs must pour some secretion into the blood either directly or by way of the lymphatics. In 1854 Kolliker (3) published a description of the microscopic structure of the adrenals and their nervous connections. He recognized the medulla and the cortex as functionally different structures and wrote, "The medullary substance of the suprarenal gland is not a true secreting gland, but rather is related to the nervous system, in which the cellular and nervous elements are in apposition."

The modern study of the physiology of the adrenals may be said to have begun with Thomas Addison (4). His classic description in 1855 of the disease of the adrenals, which has since been associated with his name, initiated a series of researches which have continued to the present day. Not only did Addison recognize the condition as a morbid entity, but he also accurately correlated it with a pathological state of the adrenals. He wrote, "The leading and characteristic fea-

tures of the morbid state, to which I would direct attention, are anemia, a general languor and debility, a remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of colour of the skin, occurring in connection with a diseased condition of the suprarenal capsule." Addison's publication (4) prompted Brown-Sequard (5) in 1856 to extirpate the adrenals from rabbits, dogs, guinea pigs and rats. The uniformly fatal outcome following bilateral extirpation led him to conclude that these glands were indispensable for life. His conclusions, however, were questioned on the basis that death might have been occasioned by the surgical procedure itself. Biedl (6) later devised an ingenius operative technique to avoid this criticism. He first removed the glands from their normal posiition and, with their blood vessels intact, attached them subcutaneously. Several days later he removed the glands through a simple skin incision, and this resulted in the prompt death of the animals. He noted also that animals so treated showed many of the signs characteristic of the clinical manifestations of Addison's Disease.

The French physiologist Vulpian (7),working at about the same time as Addison (4) and Brown-Sequard (5), discovered that the cells of the medulla and the cortex had different staining characteristics. He noted that the medulla was stained green by ferric chloride and that the blood of the adrenal vein sometimes gave a similar reaction. (It is now known that this reaction is characteristic of the secretion of the medulla.) The observations of Oliver and Schafer (8) in 1894 of the remarkable pressor effects of extracts of the adrenal medulla turned attentention to the study of epinephrine and the medullary portion of the

gland. Thereafter, for about thirty years, study of the physiology of the cortex was neglected and was overshadowed by the apparent importance of the medulla.

During this interval the medulla was thoroughly investigated. Following Vulpian's description (7) in 1856 of the iron chloride reaction of the medulla, Henle (9) reported that the medulla assumed a brownish coloration when treated with a salt of chromic acid, and this reaction later paved the way for the elaboration of the "Chromaffian System" as we know it today. The relatively high concentration in which epinephrine occurs in the adrenals rendered it relatively easy for Abel (10) to isolate the active principle of the medulla in 1899, and it was but two years until Takamine (11) and Aldrich (12) prepared the first pure crystalline l-adrenalin. The discovery of epinephrine, its isolation and the demonstration of its powerful pharmacological action focused all attention on this substance as the important product of the adrenal gland.

Takamine (11), Jowett (13), Stolz (14), Dakin (15) and others, labored to determine the structure of this hormone, and their work enabled Friedmann (16) in 1906 to establish definitely the structural configuration of this substance. These observations are of considerable historic interest since they represent for the first time the isolation and synthesis of a pure crystalline hormone. It is interesting to note that the synthesis of this hormone by Stolz (14) in 1904, and Dakin (15) in 1905 preceded the determination of its structure by Friedmann (16) in 1906.

Numerous experiments were devised and theories elaborated concerning the physiological role of adrenalin. Oliver and Schafer (8) in 1895 previously demonstrated the immediate and marked rise of blood pressure produced by the injection of a medullary extract. In 1899 a similar extract was observed by Boruttau (17) to inhibit the tonus of the alimentary tract, and Blum (18) in 1901 showed that an injection of epinephrine caused glycosuria. He noted that this was the result of a hyperglycemia produced by glycogenolysis in the liver. This was confirmed by Mann and Magath (19), who showed that the hyperglycemia did not occur after the removal of the liver. It is interesting to note that Cori (20) later showed that the mobilization of all the glycogen present in the liver could account for only a part of the glucose which appears in the circulation after an injection of epinephrine. In fasting rats he found that epinephrine caused a decrease in the glycogen content of the muscles with a concurrent increase in the glycogen store of the liver, and postulated that this was due to a break-down of glycogen in the muscles to lactic acid, which in turn was re-synthesized into liver glycogen. The further break-down of this newly formed glycogen was thought to result in the hyperglycemia seen following the injection of epinephrine. Cannon (21) in 1922 attempted to explain the function of the medulla, and pointed out that epinephrine was serviceable in lessening muscular fatigue, accelerating the coagulation of the blood, and in otherwise aiding the organism in an emergency. The preoccupation with all phases of interest in connection with epinephrine diverted attention from the problems associated with the cortex.

Soon it became apparent that the medulla was not essential for life, and increased attention was directed to the cortex. When Thomas Addison (4) noted the lesions which accompanied the syndrome of adrenal cortical insufficiency, he provided the first tangible proof of the important role played by the endocrines in internal medicine. Brown-Sequard (5) soon thereafter reported that the adrenals were essential for life. That the substance necessary for the maintenance of life actually originates in the cortex was first demonstrated on elasmobranch fish, such as the torpedo, in which the cortex is separate from the medulla. In 1913 Biedl (6) extirpated the cortex in the torpedo and observed muscular weakness, convulsion, a decreased respiratory rate, and death in three to seven days. Similar observations in 1914 by Crowe (22), Wheeler and Vincent (23) in 1917, firmly established the critical need for the adrenal cortex in survival. These workers excised one adrenal in mammals, removed half of the second adrenal and cauterized the medullary substance in the remaining half of the gland. The animals so treated survived for long periods in relatively good health, so demonstrating the relative unimportance of the medulla. In 1923 Houssay and Lewis (25) split the left adrenal of dogs, excised the medulla and ten days later removed the right gland. Their animals also appeared to remain entirely normal. Hartman et al (26) in 1928 obtained an extract which he called "cortin", and which was capable of significantly prolonging the survival time of adrenalectomized animals. Similar results were noted by Stewart and Rogoff (24), who one year later showed that the lives of completely adrenalectomized animals could be prolonged by the in-

jection of a cortical extract combined with a transfusion of saline. It was in 1931, some thirty years after the isolation of the adrenal medullary hormone (11)(12), that Swingle and Pfiffner (27) utilized lipid solvents in the manner first used in the isolation of estrogenic substances, to prepare a highly potent cortical extract. Soon thereafter, in 1933, Grollman (28) introduced a simple method of concentrating the active principle of the cortical extract by absorption on charcoal.

The isolation of the crystalline steroid hormones from cortical extracts was achieved by a number of investigators. In 1934 Kendall et al (29) announced the isolation of a crystalline substance capable of maintaining the life of an adrenalectomized animal. Wintersteiner and Pfiffner (30)(31) and Reichstein (32) also obtained active crystalline preparations. During the following three years contributions from the above laboratories finally led to the elucidation of the chemical structures of many of the cortical steroids (33)(34)(31)(35).

The first partial synthesis of a corticoid was announced in 1937 by Steiger and Reichstein (36), who used stigmasterol as the starting material for the synthesis of 11-desoxycorticosterone. As was the case with epinephrine, this compound also was synthesized before it was isolated from its source by Reichstein and Euw in 1938 (37). More recently 11-dehydrocorticosterone (Compound A) and corticosterone (Compound B) have been prepared (38)(39). In 1946 Sarret (40) in co-operation with Kendall succeeded in synthesizing 17-hydroxy-11-dehydrocorticosterone (Compound E) from desoxycholic acid. To avoid confusion with Vitamin E the name of this compound later was changed to Cortisone.

In 1941, some years before these pure hormone preparations became available, Hench (41) noted the possibility that rheumatoid arthritis was a reversible disease. It had long been known that the condition was capable of undergoing a spontaneous remission, particularly during attacks of jaundice and during pregnancy (42)(43)(44)(45)(46). On this basis Hench speculated that the factor which caused the remission was possibly an adrenal cortical hormone.

In 1930 Smith (47) demonstrated that adrenal cortical function was regulated by a secretion of the anterior pituitary. Three years later Collip (48) isolated an impure "adrenotropic" hormone which contained the adrenocorticotrophic principle in potent amounts. Pure forms of this adrenocorticotrophic hormone (ACTH) were subsequently isolated in 1943 by Li et al (49) and Sayers et al (50) from sheep and swine pituitaries. The addition of ACTH to the growing list of hormones being isolated and synthesized at this time provided still another means of studying adrenal physiology.

Selye (51) brought forth his theoretical concept of the General Adaptation Syndrome in 1946. His experimental observations led him to conclude that many seemingly unrelated diseases were due to an imbalanced elaboration of the cortical hormones, which resulted after periods of continued stress. Among such "diseases of adaptation" as he termed them, were included rheumatic fever, rheumatoid arthritis, gout, nephrosclerosis, hypertension, periarteritis nodosa and eclampsia.

In September, 1948, shortly after compound E (Cortisone) was synthesized, Hench et al (52) administered this hormone to a patient with

severe rheumatoid arthritis and striking and rapid improvement in clinical and laboratory features of the disease resulted. Subsequently in 1949 these investigators reported dramatically favorable effects on severe or moderately severe rheumatoid arthritis with Cortisone in fourteen patients, and with adrenocorticotrophic hormone (ACTH) in two patients.

These observations initiated a series of experimental and clinical studies designed to determine the function of these hormones in normal adrenal physiology, and their possible usefulness in treating disease entities.

A REVIEW OF THE LITERATURE

1. The Effects of Adrenalectomy: Adrenal Insufficiency.

Adrenalectomies have been performed on fish (6), frogs (53), birds (54), rabbits (55), dogs (56), cats (57)(58), rats and mice (55) (59). The importance of the cortex for the maintenance of the functional integrity of the organism has been demonstrated conclusively. There now remains no doubt that the cortical cells of the adrenal elaborate hormones of vital importance to the organism, for death rapidly follows excision of this part of the gland (5)(6)(53)(60). Attention is directed to the multiple disturbances which follows hypofunction or ablation of the gland.

(a) Survival Time.

Workers using extirpation techniques have noted that the survival time of animals may vary under certain circumstances. Sisson and March (6) reported that adult animals survived longer than did those of the same species which were immature. Optimum pre-operative care was found to increase the survival time in rats (55). Animals subjected to stressful situations, such as poor nutrition or abnormal temperatures prior to adrenalectomy, were noted to succumb more rapidly than those which had lived in an ideal environment.

The completness of extirpation was most important in determining the period of survival. Any fragments of the gland or accessory tissue of similar origin may hypertrophy sufficiently to permit indefinite survival of the animals (62). Some authors (55)(58) reported prolongation of the survival time of adrenalectomized animals during

pregnancy, which may be due to fetal cortical hormone passing through the placenta to the maternal tissues. Sex, however, has no prolonging effect on the survival time (56).

(b) Physiological Disturbances.

The physiology of adrenalectomized animals in adrenal insufficiency is disturbed in many characteristic ways. Some phenomena are not observed in animals surviving adrenalectomy for a short time, however, after the introduction of cortical extracts (24)(26)(27) the survival time of adrenalectomized animals could be prolonged, permitting observation of these animals for longer intervals. The changes which occurred during cortical insufficiency were observed by gradually discontinuing the administration of these extracts.

(1) Anorexia

A loss of appetite is one of the earliest symptoms of adrenal cortical insufficiency in dogs (56), cats (57)(58) and men (4). If the animal survives adrenalectomy for some time a marked inanition is usually seen.

(2) Adynamia

The increased fatigability noted by Addison (4) is seen as cortical insufficiency progresses. Muscle weakness (6)(53), which is evident in smooth as well as in skeletal muscles, is soon replaced by paralysis, or convulsions (6)(55) not unlike those seen following an overdose of insulin (55). That the observed prostration and weakness were not due to a paralysis of the muscles or their nerves, was demonstrated by Elliott when he noted that the muscles of moribund animals

could be stimulated to normal activity. Further the fact that convulsions may occur supports the thesis that adynamia is the result of impaired circulation producing a central nervous system anoxia.

(3) Temperature Regulation

The ability of the adrenalectomized animal to regulate body temperature, when exposed to a normal environment, is markedly impaired. Adequate adjustment cannot be made to either excessive heat or cold and the temperature gradually drops as the cortical insufficiency becomes more severe (63). In effect the adrenalectomized animal is poikilothermic while the non-adrenalectomized animal is hemothermic, in that it retains the ability to maintain a constant body temperature. It is thought that the inability to regulate body temperature is due to the impaired circulation and to the lowered metabolic rate (64), for it has been observed that the diminution in oxygen consumption and body temperature are directly proportional to the degree of adrenal insufficiency (65). Respiration due to muscular and circulatory failure usually becomes slow, and progresses to complete respiratory paralysis (62) and death.

(4) Circulatory Alterations

At first the pulse becomes rapid and may be irregular (62), but as the insufficiency becomes pronounced the pulse becomes slow and the heart may go into a slow auricular fibrillation (66). Cardiac failure is accentuated by the diminished cardiac output produced by the decreased heart rate and the progressive decrease in blood volume, as indicated by increased hematocrit values (67). Hypotension is com-

monly observed following adrenalectomy (64) and reflects reduced efficiency of the cardiovascular system during insufficiency.

Differential cell counts are also altered in adrenal insufficiency. It has been shown in cats that there is a relative decrease in polymorphonuclear neutrophils and a corresponding increase in the number of mononuclear lymphocytes (68).

(5) Hypersensitivity to Stress

Perhaps one of the most consistant physiological changes observed in adrenalectomized animals is the altered sensitivity to all forms of stress such as heat, cold, exercise and emotional disturbances. Adrenalectomized animals are unable to maintain their body temperature when cooled (69), and it has been reported that the metabolic rise which normally follows subjection to cold does not ocdur in adrenal insufficiency (70). Adrenalectomized animals can be thrown into acute and fatal insufficiency by subjecting them for a few hours to temperatures which the normal animal can endure with impunity (70). Such animals are exceedingly sensitive to toxins (71)(72)(83) and are very prone to infections. They succumb to disease processes which usually have only trivial effects in normal animals.

(c) Pathological Disturbances.

At autopsy adrenalectomized animals and humans show very little pathological evidence to account for the diverse symptoms seen during cortical insufficiency.

(1) Pigmentation

In clinical adrenal insufficiency the patient's skin becomes characteristically bronzed in color. This pigmentation, first des-

cribed by Addison (4), has not often been produced in animals. Harrop and Weinstein (74) reported pigmentation in an adrenalectomized monkey, which was kept alive for several weeks with cortical hormone, but other attempts to reporoduce this phenomenon in animals have been unsuccessful.

(2) Other Autopsy Findings.

Perhaps the most outstanding autopsy finding in adrenalectomized animals is the marked hyperemia of the visceral organs, and the frequent occurrence of hemorrhages into the gastrointestinal tract (75). Gastric ulcers are often seen and are usually multiple and cone shaped. Mann (75) has demonstrated that these lesions develop in the absence of pancreatic secretion and bile, and are, therefore, not due to regurgitation of these fluids.

Degenerative changes noted in the liver (76) of dogs have been thought perhaps to account for the abnormal carbohydrate metabolism of adrenal cortical insufficiency.

Hypertrophic changes have been noted in the various components of the lymphatic system. Such changes were described by Star (77), who recorded the persistance of the thymus in patients dead of Addison's disease. Jaffe (78) has commented on the similarity of the general lymphatic enlargement seen in Addison's disease, and that seen in the so-called "status lymphaticus". He calls attention to the fact that adrenalectomy in young animals stimulates growth of the thymus, while in older animals active regeneration of thymic tissue occurs. Enlargement of the lymph nodes in adreanlectomized dogs (76) and cats (79) has been described.

The heart has been observed to be filled with clots formed during life (80), which is probably a direct result of the hemoconcentration which occurs in adrenal insufficiency. Controversial evidence exists as to the effect of adrenal insufficiency on cardiac action. Dilatation of the heart has been reported (8), but more recent work has shown the heart size to decrease in chronic adrenal insufficiency (82)(83).

(d) Biochemical Disturbances.

(1) Sodium Loss

In adrenal insufficiency there is a marked abnormality in the metabolism of sodium resulting in a negative balance of this ion, a fall in the total electrolyte content of the extracellular fluid, and a shift in the distribution of the body fluids.

Loeb (84) and Harrop (85) and co-workers have shown that there is a negative balance of sodium and chloride, due to the urinary excretion of these substances in excess of their intake. This condition is reflected in a fall in the concentration of sodium and chloride in the serum and extracellular fluids.

The loss of sodium is probably the result of impaired renal function caused by the lack of the cortical hormone and is accompanied by an increased elimination of water and dehydration. The kidney fails to re-absorb a sufficient quantity of sodium to maintain the normal osmotic pressure of the extracellular fluid (86). With a fall in the concentration of the extracellular electrolyte, the extracellular fluids become hypotonic relative to to the intracellular fluid, and consequently there is a shift of water into the cells resulting in anhydremia. This

phenomenon is seen in Addison's disease and in the adrenalectomized cat (87) and dog (64). In addition the existance of a negative water balance has been demonstrated in the adrenalectomized dog (84)(85). It is thought that the water loss is the result of mechanism directly related to the excess loss of sodium in adrenal insufficiency.

The lack of cortical hormone permits excess sodium to pass into the glomerular filtrate making it hypertonic relative to the body extracellular fluids. In order to restore isotonicity, water passes from the extracellular compartment into the glomerular filtrate. This water loss, however, seems to lag somewhat behind the loss of sodium. Because of this the extracellular fluids are always hypotonic to the intracellular fluid, and water shifts into the cells in an attempt to maintain the isotonic state. With the shift of water into the cells, hydration of the specialized osmoreceptors (88), thought to be located in the region of the supraoptic nucleus, occurs. The resultant disturbance of the milieux interior of these cells is thought to suppress the liberation of pituitary antidiuretic principle, so augmenting the water diuresis (89).

(2) Potassium Retention

Following extirpation of the adrenals, there is a steady increase in the potassium level of the blood and extracellular fluids (90)(87)(91)(92). The concentration of cellular potassium in muscle also rises (93). The retention of potassium also seems to be due to a renal defect, for ordinarily the kidney can prevent its accumulation in the blood even when very large amounts are administered. Thus, in adrenal cortical insufficiency there is a dual disturbance in the renal excretion

of electrolyte. Sodium, which is normally re-absorbed in order to maintain osmotic equilibrium, is lost in excessive amounts. On the other hand potassium, which is normally excreted, is retained. The resultant hyperpotassemia may in part account for the cardiac arrythmias seen in the terminal stages of adrenal insufficiency (62).

(3) Increased Blood Cholesterol and Non-Protein Nitrogen.

Adrenalectomy is followed by an increase in the blood level of cholesterol (94). It is now thought that this increased cholestrol concentration results from failure of the adrenal to utilize it in the synthesis of the cortical hormone.

Disturbed nitrogen excretion, as well as faulty electrolyte excretion, has been noted in adrenal insufficiency. A rise in the non-protein nitrogen concentration in the blood of adrenalectomized cats has been demonstrated (95). After injections of urea or creatinine much less of these substances were excreted by adrenalectomized animals than by normal animals. Marshall and Davis (95) also observed a diminution in the excretion of phenolsulphonephthalein in adrenalectomized animals, and concluded that normal kidney function was dependent upon the integrity of the adrenals or a product of their secretion. Many subsequent writers have confirmed their results (96)(97)(98)(99).

(4) Carbohydrate Metabolism

Hypoglycemia has been demonstrated in adrenalectomized dogs (100) and in patients with Addison's disease (101). The latter also show an increased sensitivity to insulin (102). Liver glycogen reduction, concomitant with hypoglycemia, has been described (101), and in some

instances the liver glycogen has completely disappeared following adrenalectomy (103). That the hypoglycemia was in no way related to absence of the medullary hormone has been shown by the experiments of Houssay and Lewis (25). In animals in which no medullary tissue was demonstrable, they found the blood sugar to be normal. These observations were later confirmed by Boggild (104), who noted no changes in the elevated blood sugar levels of depancreatized rats following the removal of the adrenal medulla. On the basis of these observations it has been concluded that the hypoglycemia and reduced liver glycogen content are due to adrenal cortical insufficiency. Further it appears that in the normal organism the glucose content of the blood is maintained at relatively constant levels by the antagonism between the cortical hormones and the insulin produced by the pancreas.

11. The Effects of Cortical Extract Administration.

(a) In Adrenal Insufficiency.

When the adrenal cortical hormone is injected into adrenalectomized animals or patients with Addison's disease, the characteristics of adrenal insufficiency can be prevented, or eliminated if already developed.

Stewart and Rogoff (24) and Hartman (26) demonstrated that cortical extracts were capable of prolonging the survival time of adrenalectomized animals. Swingle and Pfiffner (27) later extracted a potent substance from the cortex, which counteracted the effects of adrenal deprivation, and permitted adrenalectomized animals to survive indefinitely.

Loeb (84)(105) and Harrop (85) had demonstrated that patients with Addison's disease and adrenalectomized animals lost large quantities

of sodium and chlorine in the urine. Although the animals survived indefinitely with elevated dietary intake of sodium (84)(85)(106)(107), in most instances such a regimen was insufficient to permit resumption of normal activities. Thorn (108) and co-workers demonstrated that adrenal cortical extract was capable of restoring the electrolyte balance in patients with Addison's disease. Serum sodium levels returned to normal and the concentration of serum potassium was diminished. These electrolyte changes were accompanied by an increase in plasma volume and extracellular fluid, and a concomitant rise in blood pressure (82). Renal function improved and, if elevated, the blood non-protein nitrogen returned to normal (108). In addition body weight increased and muscular strength improved, but there was little change in pigmentation.

Cortical extracts have been reported to restore to normal the lowered basal metabolic rate of adrenalectomized animals (109), and to elevate the fasting blood sugar levels (110), which counteracts the hypoglycemia produced by adrenalectomy. The injection of the cortical hormone increases glycogen storage in the liver. This and the circulatory improvement may account for the postponement of fatigue (111) seen following these injections. Further it has been reported that the administration of the cortical hormone produces a lymphopenia (112).

(b) On Normal Animals.

Similar effects with respect to electrolyte metabolism have been produced in normal animals and humans following the administration of cortical extracts. A retention of sodium and an increased elimination of potassium have been demonstrated in normal human beings and in dogs (108)(113)(114)(115). Lymphoid tissue and circulating lymphocytes diminish following the employment of active extracts (116).

Striking changes in carbohydrate metabolism have been noted following the injection of adrenal cortical extracts. The early contention of Britton (110) that extracts of the cortex elevate the carbohydrate stores of adrenalectomized animals above normal have been amply confirmed. When given to fasting normal rats, these extracts cause an elevation of the blood sugar and a marked deposition of liver glycogen. Accompanying this action is a marked increase in the excretion of urinary nitrogen indicating that the probable source of the carbohydrate is from protein (118)(117)(116).

111. The specific Hormone Preparations (The Cortical Steroids).

(a) Introduction

The appearance of fairly potent cortical extracts was quickly followed by the isolation from them of a number of steroid hormones (29)(30)(31)(32). Thus far about thirty steroids have been isolated from the adrenal cortex in the chemically pure state. Remaining after the separation of these compounds is the so-called "amorphous fraction", which is relatively more water soluble, and which retains a very high proportion of the activity of the original tissue. Many of the steroids isolated from the gland may represent intermediates in the synthesis of the cortical hormone, or may be artifacts arising from the manipulations of the chemist. The work of Grollman (119) and the more recent work of Haines (120) demonstrate quite clearly that the method of handling the tissue has a marked influence upon the composition and the amounts of the steroids in glandular extracts. The latter worker showed that an increased yield of 17-hydroxycorticosterone was obtained from glands

frozen rapidly after death of the animal than from glands allowed to stand at room temperature.

(b) The Chemistry of the Cortical Steroids.

The crystalline compounds that have been isolated from the adrenal cortex are similar to cholesterol, and all contain a cyclopentenophenanthrene (121) ring system. It is because of this fact that they are called steroids. Other steroid compounds are the bile acids, cardiac aglucones, sapogenins and some of the sex hormones such as testosterone.

The activity and physiological properties of the adrenal steroids vary in accordance with their chemical structure, which is related to that of allopregnane (figure 1). The parent compounds of all steroids are saturated nuclear hydrocarbons, but the steroids themselves usually have double bonds between the fourth and fifth carbons. It has been pointed out by Selye (122) that a two carbon atom side chain at carbon seventeen is essential for corticoid activity.

Chemically three groups of physiologically active steroids are recognized.

(1) The Desoxy- Group

This group of steroids are characterized by the absence of an oxygen molecule or hydroxyl group at the eleventh carbon. Desoxycorticosterone (figure 1) the most important member of the group has been synthesized (36) and is capable of maintaining the life of adrenalectomized animals and patients with Addison's disease. Another related compound is 17-hydroxy-11-desoxycorticosterone (Reichstein's Compound S). The action

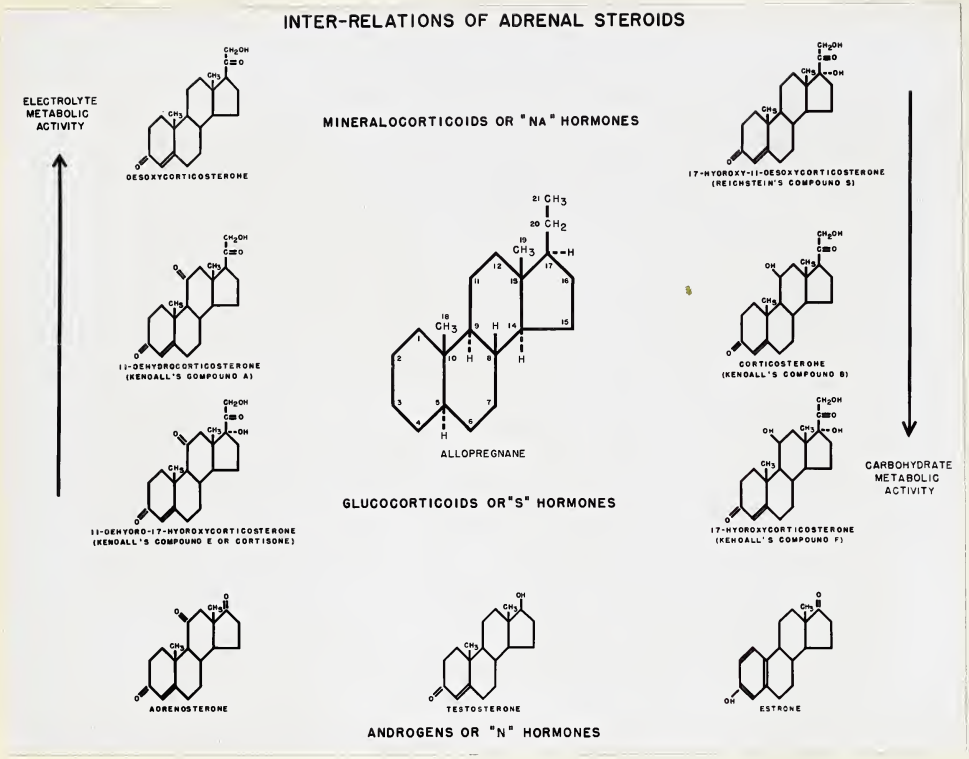


Figure 1. Inter-Relations of Adrenal Steroids.

The chemical structures of some of the adrenal steroids are shown in relation to the basic structure of allopregnane. Its individual carbon atoms are numbered as a guide for determining the chemical differences indicated in the text. The alpha and beta hydrogens are given a spatial position by the use of dotted and solid lines respectively. The former is assumed to be behind the plane of the paper, while the latter is in front. Metabolic activity of the compounds is indicated by the vertical arrow, the compound having the greatest activity being alongside of the arrow head.

of the Desoxy group appears to be predominantly concerned with the regulation of electrolyte balance, and hence is often referred to as the "sodium-retaining" group or "Na" hormones of Albright (123); the Na merely being the chemical symbol for the substance retained. Selye (122) refers to this same group of steroids as the mineralocorticoids.

(2) The 11- and 11, 17-Oxysteroid Group.

Structurally, this group of steroids is very closely related to the "Na" hormones (see figure 1), differing from the latter in that an oxygen or hydroxyl group is present at the eleventh carbon, which markedly alters the metabolic activity of these compounds (124). Early investigations have indicated that adrenal steroids having an oxygen atom at the eleventh carbon position exerted a definite influence on the metabolism of carbohydrate, fat and protein, and over lymphoid tissue and circulating eosinophils. Included in this group of hormones are 17-hydroxy-11-dehydrocorticosterone (Compound E or Cortisone), and 17-hydroxycorticosterone (Compound F), and because of their influence on "sugar metabolism" they have been designated the "S" hormones by Albright (123). It has been demonstrated recently by Selye (51) that the 11-oxysteroids and the 11, 17-oxysteroids (glucocorticoids) are important in protecting the organism against stress.

(3) The Adrenal Androgens.

It is thought that the adrenal androgens exert an effect on nitrogen balance similar to that of the testicular androgens (testosterone figure 1), hence they have been designated by Albright (123) as the "nitrogen retaining" or "N" hormones. Generally speaking a side chain at carbon seventeen is detrimental to these compounds (122), and they are

characterized by an oxygen at the eleventh carbon. Adrenosterone (figure 1) is presumed to be one of this group of hormones, and has been isolated from the urine of females as well as males in increased quantities in patients with "virilizing" adrenal tumors (125).

It should be emphasized that such a definite distinction between groups as indicated apparently does not in fact exist, for it has been noted that there is some overlapping of function of these steroids. Cortisone, which is an "S" hormone, has been reported to induce sodium retention (126) and is often followed by hirsutism when administered to patients with intact glands (127). These effects are usually attributed to the "Na" and the "N" hormones respectively. Further, the same cortical steroid may promote, as well as inhibit, glucose utiliziation (128), or produce anabolism as well as catabolism (129).

The chemical configuration which apparently determines the predominant actions of a particular crystalline preparation from the adrenal cortex is the presence or absence of an oxygen atom at carbon eleven. When the oxygen is absent the predominant action is on electrolyte metabolism, and when it is present on carbohydrate and muscle metabolism (130).

(c) The Effects of Specific Cortical Steroid Administration.

The general description given of the action of the relatively crude extracts of the adrenal cortex in restoring the health of adrenalectomized animals may now be supplemented by an account of the effects which result from the administration of crystalline fractions of the cortical extract.

(1) Desoxycorticosterone.

Desoxycorticosterone, prepared synthetically as an acetate (hereinafter called DOCA), is a potent and effective regulator of elec-

trolyte metabolism and has no demonstrable direct effect on protein or carbohydrate metabolism in man and little, if any, in experimental animals (131)(132).

The most outstanding action of DOCA is upon sodium, potassium and water metabolism (111)(133). DOCA causes an increased retention of sodium and water, and an increased excretion of potassium (134). Plasma volume and serum sodium levels are increased while the serum potassium levels are reduced (135). Following administration of DOCA intracellular potassium is decreased and that of sodium increased. Chlorine is also retained, but the fact that sodium salts other than sodium chloride are effective in the treatment of patients with Addison's disease suggests that the retention of sodium is primary, and that the chloride changes in general follow those of sodium (125).

In patients with adrenal insufficiency, DOCA restores the serum sodium and potassium, and the plasma volume to normal levels and elevates the blood pressure (136)(137). The drug is of value in the management of adrenal insufficiency (138)(139)(140) and such patients are often able to resume essentially normal activity by the administration of DOCA and sodium chloride alone.

Presumably the major site of action of the compound is on the renal tubule (111). However the effects are not all renal for the steroid appears to reduce the permeability of tissue generally (111)(141). The mechanism of the action of DOCA is to restore the ability of the tubules to re-absorb sodium salts and to excrete potassium (115)(102). Normally the extent of re-absorption of sodium is delicately adjusted by the kidney so that a sodium balance is maintained. Because of the amount

of sodium retained determines to a large extent the volume of extracellular fluid, it follows that the regulatory action of the kidney in the rejection or re-absorption of sodium is the main mechanism by means of which the body maintains a relatively constant extracellular fluid volume. Administration of DOCA, therefore, in causing a retention of sodium results in an increased extracellular fluid volume (142). In large doses DOCA may produce edema, pulmonary congestion, hypertension and cardiac dilatation and failure (111)(102)(133) with perhaps sudden death (136)(143).

The manner in which DOCA induces these ill effects is not certain. The rapid increase in plasma volume (137) and, as a result of this, the extra burden thrown upon the cardiovascular system is suspected of being an important factor.

Depression of the potassium concentration of the body fluids may be a lethal factor in some instances (133). It has been shown that the adminstration of DOCA to animals may lower the potassium level to the point where paralysis develops (111). Occasionally hypopotassemia induced by the drug gives rise to weakness and to electrocardiographic changes (133).

In addition to its effect on the renal control of electrolytes, DOCA also seems to exert a regulatory effect on the electrolyte composition of sweat. Conn (144) and his co-workers have demonstrated that DOCA induces a sharp fall in the concentration of sodium and chloride in the sweat, and an increase in the concentration of potassium.

Interestingly enough, and contrary to common belief, the administration of DOCA to dogs for long periods has been demonstrated to

produce a condition resembling diabetes insipidus (145). The water intake, especially if salt is administered, is increased from six to tenfold, and the output of a low specific gravity urine rises accordingly (146).

DOCA does not correct the defect in carbohydrate metabolism which is evident in patients with Addison's disease, and some deaths reported associated with the use of DOCA may have been due to hypoglycemia (139)(143).

The question might reasonably be raised as to whether DOCA is the substance normally responsible for electrolyte regulation in man. Following adrenocorticotrophic hormone stimulation in normal human subjects, there is a pronounced retention of sodium and chloride, with a rebound following cessation of therapy (147). The magnitude of these changes is in every way comparable to the action of DOCA. A corresponding change has not been noted with any other adrenal steroid, yet in larger amounts compounds E and F do act similarly. The physiological role of desoxycorticosterone remains unsettled.

(2) Cortisone (11-Dehydro-17-Hydroxycorticosterone or Compound E)

(a) Effects of Cortisone on Carbohydrate Metabolism.

Early investigations indicated that Cortisone and other adrenal steroids having an oxygen atom at the eleventh carbon position exerted a definite influence on carbohydrate metabolism (148)(149)(150).

Cortisone given to normal rats forced fed with a high carbohydrate diet produced a transient hyperglycemia and glycosuria (151). When administered to partially depancreatized animals with intact adrenal glands, it intensified the glycosuria, and when given to partially

depancreatized, adrenalectomized animals glycosuria reappeared (148) (118)(152). Because of concomitant increases in the excretion of nitrogen and ptassium, it was at first reasoned that Cortisone and the other 11-oxysteroids stimulated gluconeogenesis by manufacturing the glucose at the expense of tissue protein (118). Later studies, however, suggested hat gluconeogenesis may not be accomplished by the catabolism of body protein, but by a process of blocking protein synthesis (anti-anabolic effect) whereby amino acid radicles were diverted to pyruvic acid and thence to glucose (123)(152)(153). When adrenalectomized (154)(155) or hypohesectomized animals (156) were subjected to phlorhizin and then injected with cortisone, an increased excretion of glucose and nitrogen occurred, indicating that the hormone is capable of replacing the gluconeogenic function of the adrenal gland. The hormone was found to counteract effectively the hypoglycemic effect of insulin (148)(157)(158) and to promote the deposition of glycogen in the liver and the muscles (149)(159)(160)(161). In patients with Addison's disease in whom electrolyte balance was maintained with DOCA, the administration of cortisone corrected the abnormal carbohydrate metabolism; the fasting blood sugar was raised, the respiratory quotient decreased and the threshold for hypoglycemic reactions increased.(162). In subjects with co-existing Addison's disease and diabetes mellitus, the diabetes was intensified following the daily administration of cortisone (163).

(b) Effects of Cortisone on Electrolyte Metabolism.

Cortisone given to human subjects over long periods has little overall effect on electrolyte metabolism (147)(164). In moderate dosage

(100 mg. daily), cortisone induced minimal or no alterations in balances for nitrogen, calcium, phosphorus, sodium, chloride and potassium, and in the concentrations of electrolytes in the extracellular fluid as measured in the plasma. Larger doses regularly induced a negative balance for nitrogen and ptassium, whereas augmentation of nitrogen excretion was slight or absent when the dose of cortisone was moderate (52)(147). Large doses had variable effects on the excretion of sodium and chloride. The most common effect was a retention of these ions at first followed later by increased excretion (149). According to Thorn (152) cortisone and the related 11-oxysteroids exert a weak sodium retaining effect, about one-thirtieth of that produced by DOCA. However under certain conditions, as in the presence of excessive sodium retention induced by DOCA, cortisone may act in competition with DOCA and cause increased sodium excretion (153). Cortisone was found to increase the excretion of potassium and phosphorus in partially depancreatized adrenalectomized rats. Its administration to normal subjects and patients with gout produced increased renal clearance of uric acid resulting in the excretion of large quantities of urates (152). Also young rats receiving the hormone exhibited a decrease in the phosphatase activity of the bone epiphyses (165).

(c) Other Metabolic Effects of Cortisone.

Urine concentrations of corticosteroids were increased initially with large doses of cortisone, but with continued administration, the amount excreted remained elevated or declined toward normal values (52) (147). Administration of cortisone was followed by a prompt and striking fall in urinary 17-ketosteroid values. This suggested that the hormone depressed some of the functions of the adrenal cortex (52)(147).

(d) Effects of Cortisone on the Organism.

Cortisone given to young rats suppressed their growth and development (111), and in both sexes caused marked atrophy of the adrenal and thymus glands (166). Similar atrophy was noted in the spleen and lymph nodes (123)(167), which suggested that the hormone might have a depressant effect on certain types of lymphatic tumors (168). Subsequently it was found that adrenalectomized rats showed an augmented susceptability to "transplanted lymphatic leukemia" indicating that the adrenal secretions might have an inhibitory effect upon the development of this disease (169). Heilman and Kendall (168) later demonstrated that transplants of a highly malignant mouse tumor, diagnosed as lymphosarcoma, failed to grow if the recipient mouse received cortisone. Pronounced regression of these tumors, even though well developed, occurred with the administration of the hormone.

Cortisone and the other 11-oxysteroids have the capacity of increasing muscle strength, endurance and efficiency in adrenalectomized animals (170)(171)(172), but these effects have not been observed in animals with intact adrenal glands. Physiological resistance to stress and shock is greatly enhanced in adrenalectomized animals when cortisone is administered. The substance has been reported to be highly effective in protecting such animals against low temperatures (165).

A striking sense of well being is exhibited by most patients early in the period of cortisone administration (52)(147), although the degree of mental stimulation varies somewhat with the size of the daily dose given (173). Usually there is definite improvement in the mental attitude of patients receiving the hormone, but some initially depressed

and pessimistic, may become frankly euphoric. Cortisone tends to mask pain, and death may remain unsuspected and unheralded by the usual impending painful symptoms (174).

Other effects noted include decreased libido in the male (147) and a return of febrile individuals to the afebrile state (175). Appetites usually improve, and with the increased food consumption there results a corresponding gain in weight (52)(147).

(e) Effects of Cortisone Reflected in Laboratory Tests.

Elevated erythrocyte sedimentation rates are reported to be significantly decreased within a few days after cortisone administration is started (52)(173). Improvement has been noted in the erythrocyte count and the hemoglobin levels (173), particularly when anemia is present on commencing therapy with the hormone (52). Small but significant increases in the total number of circulating leukocytes have been noted during the protracted administration of cortisone, but no significant changes in the number of lymphocytes or eosinophils occurred during or after long term administration of the hormone (147). A lysis of fixed lymphatic tissue, a transient decrease in circulating lymphocytes and a marked decrease in circulating eosinophils from the blood have been noted during short period administration of the hormone (152).

No significant changes in the electrocardiogram pattern of patients treated with Cortisone have been noted (173). Acceleration of the alpha waves of the electroencephalogram have been observed (173). High doses of cortisone may produce a metabolic alkalosis due to increased urinary excretion of potassium and chloride. In such cases electrocardiographic changes characteristic of hypopotassemia may appear.

The T wave may be lowered and the ST segment and junction depressed. Concomitant with these electrocardiographic changes, lowered serum chloride and increased CO_2 combining power of the blood are found (147).

In certain instances where the basal metabolic rate was raised (due to causes other than hyperthyroidism), it became normal following cortisone administration (147).

(f) Other Hormonal Effects of Cortisone.

Objective signs of hyperadrenalism have occurred in some cases where cortisone has been given for extended periods and in large doses. Rounding of the facial contour (moon-like facies) is one of the earliest signs of cortisone excess, and may or may not be associated with some fuzzy hair growth (147)(176). Disturbances of the menstrual cycle usually in the form of amenorrhea or irregular menses may occur with prolonged administration (147). Transient edema, usually pretibial, has occurred, but disappears on reduction of the dose or following the use of saline diuretics (52)(176). Manifestations of a mild Cushing's syndrome characterized by acne, hirsutism, rounded facial contour, amenorrhea, stria of the skin and mental depression may appear, but disappear on cessation of cortisone (147). Pre-existing diabetes may be intensified, thus necessitating an increased daily insulin requirement (173).

IV. The Nature of the Adrenal Hormones.

(a) Introduction.

In discussing the nature of the hormones produced by the adrenal cortex, certain mechanisms of hormone production are assumed. Of prime importance are those hormones produced by the pituitary, which act on "target" organs, causing them to produce characteristic hormones which in turn act on the peripheral tissues. Such pituitary hormones are called trophins, and in particular those which act on the adrenal cortex are called adrenocorticotrophins.

The exact nature of the hormones secreted by the adrenal cortex still remains obscure. Present estimates of the number and character of the steroids produced by the gland are based on indirect evidence, such as the types of steroid isolated from the gland after death, and comparisons between metabolic changes induced by the adrenocroticotrophic hormone and those produced by the crystalline cortical preparations at present available.

(b) Theories Regarding the Nature of the Secretion

A number of theories have been postulated to explain the existance of so large a number of steroid compounds, and the multiplicity of metabolic patterns which an organism may exhibit under different environmental conditions.

(1) The Multisteroid Concept.

In the early phases of adrenocortical investigation, Selye (51)(77) postulated the existance of four distinct pituitary trophins which produced four separate types of cortical hormones. According to this view the adrenal cortex is stimulated by a "glucocorticotrophin" to secrete

steroids influencing carbohydrate metabolism ("glucocorticoids"); by a "mineralocorticotrophin" to secrete desoxycorticosterone or DOCA-like steroids ("mineralocorticoids"); by a "lipocorticotrophin" to secrete steroids which induce deposition of fat in the liver ("lipocorticoids"); and finally by a "testocorticotrophin" to secrete androgens ("testocorticoids"). He suggests that the components of adrenal cortical secretion may vary independently according to the requirements of the organism, but such secretion remains yet to be proven.

(2) "N" and "S" Hormone Concept.

Albright et al (123)(178)(179)(180) in interpreting results obtained from mouse experiments have suggested that the adrenal cortex secretes a "S" or "sugar" hormone (Cortisone-like compound also designated as 11, 11-oxysteroid), which is under the influence of a pituitary adrenocorticotrophin, and an "N" hormone having the anabolic properties of an androgen, which is under the influence of the pituitary luteinizing hormone.

Urinary 17-ketosteroids (which are structurally similar to adrenal androgens and have an oxygen on C17) have been regarded by Albright (123)(178) as metabolic end products of adrenal androgens and, therefore, are an index of adrenal "N" hormone secretion. Urinary "corticoids" (steroids having one or more characteristics of the cortical hormones) are regarded by Albright as an index of "S" hormone production (178).

The lack of parallelism of these two indices, both in normal men exposed to stress and in the endocrinopathies, are regarded as evidence in support of the dual nature of the adrenocortical secretion.

The methyl testosterone-induced depression of 17-ketosteroid excretion in the castrate is interpreted by Reifenstein and Albright (180) to mean that the exogenous androgen inhibits the release of pituitary luteinizing hormone (L. H.), which is the gonadotrophin presumed to stimulate the adrenal cortex to secrete androgens. Further, the contrasting pattern of metabolic dysfunction and urinary excretion of steroids in Cushing's syndrome and the adrenogenital syndrome (123) exemplify hypersecretion of "S" and "N" hormones respectively. Albright presumes that each of these pathologic states is an exaggeration of one of the dual functions of the normal gland.

In the mouse there can be little doubt that a special X zone of the adrenal cortex secretes androgens under the influence of a gonadotrophin. However, there has been no convincing experimental evidence brought forth to demonstrate that luteinizing hormone (L. H.) acts directly on the adrenal cortex of species other than the mouse. In addition a compensatory increase in the secretion of "N" hormone does not prevent the development of eunichoid symptoms observed following castration of the human male (195). The importance of the pituitary regulation of the androgen secretion of the adrenal cortex is at present unknown.

(3) The Autonomy Concept.

In the rat it has been noted that following hypophysectomy the zona fasciculata and zona reticularis of the adrenal cortex atrophy rapidly (181), and no longer stain histochemically for ketosteroids, whereas the zona glomerulosa shows a compensatory hypertrophy. Also in the rat it has been shown that the zona fasciculata produces steroids affecting

sodium and water metabolism (182). These observations together with the fact that the hypophysectomized rat in contrast to the adrenalectomized rat can survive without salt therpay prompted Swann (182), Greep and Deane (181)(183)(184) to conclude that in the rat the zona gomerulosa (outer zone) autonomously elaborates a hormone which regulates electrolyte metabolism, whereas the zona fasciculata, which is the zone producing sugar and protein hormones, is subject to pituitary control. Supporting evidence for this concept was presented when Ingle et al (185) and Bergner and Deane (186) observed that ACTH had little effect upon electrolyte metabolism in the rat, in that sodium retention was not observed. They also noted that hypophysectomized rats did not lose vital amounts of sodium and chlorine (187) as does the adrenalectomized animal, and suggested that the secretion of active sodium retaining steroids by the adrenal cortex was independent of ACTH production by the pituitary.

On the other hand in man ACTH has been found to cause marked salt retention (188). This may have been due to the type of ACTH used, for Mason et al (189) using Li's homogenous material got no retention of sodium and chlorine in a study on a normal woman. Further, this concept fails to explain why panhypopituitarism in animals or patients impairs their ability to adjust to situations of reduced or excessive electrolyte intake.

Sayers (190) uses the following explanation to embrace more adequately the experimental facts. In the absence of the pituitary and provided dietary conditions are optimal, the adrenal cortex secretes a small unfluctuating quantity of cortical hormone which is sufficient to

maintain electrolyte balance in panhypopituitarism with its associated low metabolic activity. However, when the regulatory mechanisms are taxed by dietary inadequacies or excesses, the adrenal cortex is incapable of meeting the situation with an increased rate of secretion of the cortical hormone.

(4) The Unitarian Concept.

This point of view suggested by Sayers (191) regards the secretion of the adrenal cortex to be of fixed composition and under the control of a single trophin (ACTH). The rate of secretion is thought to vary with the needs of the peripheral tissue, which determine the blood levels of the cortical hormone under any circumstances. In stress, it is suggested that the blood level of the cortical hormone is diminished through an increased peripheral tissue utilization of that substance. Further it is postulated that the pituitary responds to the reduced titre by discharging ACTH at an accelerated rate, which in turn results in an increased production of the cortical hormone. More revolutionary perhaps than the pituitary-adrenal relationship described is the suggestion that perhaps a single steroid can account for all the metabolic activities of the gland.

At present this suggestion is open to question and a final decision awaits the accumulation of more experimental evidence. There are, however, many workers who believe that there are at least two major hormones produced by the adrenal cortex, the 11, 17-oxysteroids and the desoxycorticosteroids, which can account for the diabetogenic, as well as the sodium retaining properties of ACTH. On the other hand, it has been recently demonstrated by Forsham et al (126) that cortisone (a carbohy-

drate regulating hormone) can induce a small but significant sodium retention in patients with Addison's disease. This would seem to suggest that one steroid could account for the results obtained when the gland is stimulated with ACTH, but it is difficult to concede that the function of the adrenal is controlled by one trophin, because the salt retention produced by cortisone is significantly less than that produced by ACTH.

Although it is possible that the regulation of the many metabolic functions under adrenal control is effected by a single hormone, it is perhaps more likely in view of the special attributes of the different groups of steroids that more than one type of hormone is secreted by the adrenal cortex under normal circumstances, all arising from a common source (Compound F). It also appears probable that some unknown steroids of high biological activity may exist, since the effect of potent adrenal cortical extracts cannot be accounted for entirely on the basis of their known steroid content.

In opposition to the unitarian concept, most clinical investigators believe that the cortex also produces an adrogenic hormone. However, the data presented to explain this view may be as easily explained on a basis of metabolic degradation (195). Administration of cortisone has been shown to result in an elevated excretion of 17-ketosteroids in patients with Addison's disease (126), and in addition produced mild hirsuitism in females with intact adrenals (127). This evidence, coupled with the fact that 17-ketosteroids having an oxygen on C11 have been isolated from the urine (192)(193), would seem to suggest that the androgens may arise from the degradation of the cortical hormone.

On the other hand the high androgen levels seen in the adrenogenital syndrome cannot be explained in this manner. The androgens here may be the result of a neoplasm, or arise from an abnormal secretory activity of the adrenal gland. Another possibility could be that the mechanisms normally concerned with the degradation of the cortical hormone have been altered to produce androgenic substances at an abnormally high rate.

Because of the confused state of the literature concerning this problem and the lack of convincing evidence in favor of any one concept, it has been decided by the author for the sake of simplicity to regard the adrenal cortex as the origin of three types of hormones - the "S" and the "N" hormones of Albright's (123)(178) classification, and the "Na" hormones (mineralocorticoids) postulated by Selye (51)(177).

V. Measurement of Adrenal Cortical Activity.

Increased or decreased activity of the adrenal cortex is not readily measured in a direct manner. Instead many indirect methods are utilizied to assess cortical acitivity. Most important are those changes which are noted in (a) the adrenal cortex, (b) the organism and (c) the urinary excretion of steroids.

(a) Changes in the Adrenal Cortex.

(1) Gross Changes.

Increased cortical activity due to ACTH administration has been shown to be reflected in weight increases of the adrenal, proportional to the dose used (49)(50). Further indications of adrenal hyperactivity are seen in color changes of the gland itself from yellow

to brown due to the depletion of lipids (194) and in the appearance of hemorrhagic areas on the surface of the gland.

(2) Histochemical Changes.

Sayers (195) has noted in a recent review of the subject that there is a remarkable parallelism between the density of lipid stained with Sudan or Scharlach R stains and the total concentration of cholesterol in the adrenals. In general, lipid depletion denotes hyperactivity, and lipid accumulation hypoactivity of the adrenal cortex (194).

(3) Chemical Changes.

(a) Adrenal Cholesterol.

Chemical constituents of the gland tissue also vary with changes in secretory activity of the cortex. The cholesterol content of the gland, as measured by the Sperry-Schoenheimer method (196), is depleted by ACTH administration and this change is synchronous with metabolic changes which are characteristic of adrenocortical hyperactivity (194). It has been reported too in hypophysectomized rats that the adrenal cholesterol is inert and fixed at a concentration which is higher than normal (195). This data, together with the fact that cholesterol is closely related chemically to the adrenal steroids, would suggest that cholesterol is the precursor of the cortical hormone or hormones. This supposition has been further reinforced by the recent observation of Hechter et al (197) that the adrenal gland when perfused with cholesterol is able to introduce an oxygen at the eleventh carbon.

Stress (198) and ACTH (199) have been shown to deplete the content of cholesterol of the adrenal gland by fifty percent in three hours, and cholesterol determinations have been used as a supplement to gland weight in estimating adrenocortical activity.

(b) Adrenal Ascorbic Acid.

Adrenal ascorbic acid has similarly been demonstrated to decrease with increased adrenocortical activity (199). As with cholesterol, the absence of the pituitary causes the concentration of adrenal ascorbic acid to remain unchanged in response to stress (198). Although the exact functions of ascorbic acid remain obscure, there is a parallelism between the concentrations of cholesterol and ascorbic acid in the adrenals (195). However, Sayers (195) points out that levels of adrenal ascorbic acid must be employed with caution as indices of adrenal cortical function, for in acute stress in animals with nutritional defects or in chronic experiments involving malnutrition, other factors than the rate of secretory activity of the adrenal cortex may play a part in detemining the ascorbic acid level in the gland. For instance, impaired synthesis of the vitamin rather than increased cortical activity may lower the level of adrenal ascorbic acid in malnourished animals subjected to stress.

(b) Changes in the Organism.

(1) Lymphocytes.

It has been observed by Dougherty and White (200) that circulating lymphocytes are under the regulatory control of the adrenal cortex. This observation has provided an index of adrenal cortical function, which is particularly valuable in that measurements can be made using living animals. A lymphocytopenia is initiated by the discharge of ACTH from the pituitary (201) and is mediated by those steroids having an oxygen on cabon eleven (200)(201)(188). Neither stress nor ACTH will produce a lymphocytopenia in the adrenalectomized animal (200)(201), or in the patient with Addison's disease (188). Therefore,

failure to induce lymphocytopenia with ACTH may be taken as an indication of adrenocortical deficiency (188). It has been postulated by many workers that the lymphocytosis occuring in adrenalectomized animals (68)(200)(201), and in the patient with Addison's disease (202), is due to the low blood titre of the adrenocortical hormone. Conversely the lymphocytopenia seen in Cushing's syndrome (202) is probably the result of an elevated titre of the cortical hormone.

It should be pointed out that circulating lymphocytes can be employed as an index of adrenocortical function only with certain reservations, for a number of factors other than adrenal cortical activity determine the number of lymphocytes circulating in the blood at any given moment. Among these are included a splenic discharge of lymphocytes (203), and lympholytic agents such as x-irradiation (204) and urethane (205), which may be a part of the therapy of the individual on whom lymphocyte determinations were being made.

(2) Eosinophils.

Probably the most useful index of adrenocortical function is based on the observation of Hills et al (206) that the number of circulating eosinophils is determined by the activity of the adrenal cortex. There is an eosinopenia following ACTH administration (207), which is less variable than the lymphocytopenia previously mentioned (188). Many workers have shown that stresses such as labor (208), eclampsia (208), surgery (208), epinephrine injection (209)(210), insulin injection (209) and electroshock (211), produce an eosinopenia in man. Absence of an eosinopenia following ACTH administration is indicative of adrenocortical insufficiency (212). Epinephrine induces an eosinopenia

through release of ACTH by the pituitary (213), which in turn stimulates the adrenal cortex to increase the production of adrenal steroids related to 17-hydroxy-corticosterone (206)(210). The increased production of these steroids leads to a rapid fall in the level of circulating eosinophils (206), which is greatest about four hours after the injection. In the absence of adequate anterior pituitary or adrenocortical function, this change will not occur upon administration of adrenalin. While the eosinophil test described by Thorn et al (212)(214) is perhaps the most practical measure of adrenocortical activity in man, it should be interpreted with caution, as factors other than the secretion of the adrenal cortex may influence the level of circulating eosinophils. An eosinopenia can occur in infectious diseases, even in patients with Addison's disease (215), and it has been reported that large doses of epinephrine can induce an eosinopenia even in the absence of the adrenal cortex (195).

(c) Urinary Steroids.

Assays of steroids appearing in the urine, which have one or more characteristics of the cortical hormones (corticoids), are performed on crude urinary extracts. Corticoids having similar biological properties, which are determined by bioassay are called biocorticoids, and those which are determined by a chemical means are referred to as chemocorticoids.

(1) Urinary Biocorticoids.

The injection of ethylene dichloride extracts of urine into adrenalectomized animals increases deposition of glycogen in the liver (216)(217), prolongs life (216), increases survival time after exposure to cold (216)(218), improves work performance (219) and reduces suscepti-

bility to water intoxication (220). These responses are characteristic of the cortical hormones, and their occurrence following injection of urine extracts has led to the belief that the biologically active substances in the crude extracts are cortical steroids.

The properties of "cold protection" (218) and liver glycogen deposition (217)(221)(222) have been made the basis of quantitative determinations of urinary biocorticoids. Close correlations between such determinations of biocorticoid excretion and the activity of the adrenal cortex as judged by clinical criteria has shown biocorticoid excretion to be a relatively good index of adrenocortical activity. The methods of assay are time consuming however, and in many centers have been replaced by urinary chemocorticoid determinations.

(2) Urinary Chemocorticoids.

The assay techniques in use at present utilize the solubility as well as the chemical characteristics of the cortical steroids. Urine is extracted with a suitable solvent, such as ether or chloroform, or a mixture of these two reagents, and the extract is washed with aqueous alkali to remove acids and phenols. Chemocorticoid analysis may be made on the resulting neutral extract (223), or after further fractionation between benzene and water (224), which separates 17-hydroxy-corticosterone and cortisone-like substances from the less water soluble compounds such as desoxycorticosterone. Further fractionation can be carried out into ketonic and non-ketonic fractions using Girard's reagent T (224). Several chemical reactions may be employed on one or more of these fractions.

(a) Phosphomolybdic acid is reduced by steroids containing a primary or secondary alpha ketol group, an alpha, beta unsaturated 3-ketone group, or both these groups (225).

(b) Copper is reduced by steroids having an alpha ketol group.

(c) Formaldehyde is generated by the reaction of steroids having an alpha ketol or glycol side chain, with periodic acid.

A method using this reaction was first described by Lowenstein (226), who treated a urine concentrate and periodic acid mixture directly with chromogenic acid. Daughaday et al (227(228) improved this method by distilling off the formaldehyde using micro-distillation apparatus, and developing color in the distillate with the addition of the chromogenic acid.

The above reactions, it should be noted, are not specific for cortical steroids, and do not separate completely the non-active from the active steroids. Blood (223) and other organic substances normally present in tissue may react to produce falsely elevated results. However, the methods outlined for the determination of urinary chemocorticoids lend themselves to routine laboratory use, as they are relatively simple and less time consuming than the methods of biocorticoid assay.

(3) Urinary 17-Ketosteroids.

The 17-ketosteroids comprise a group of steroid compounds which, as the name indicates, have in common a ketone group at position seventeen of the steroid nucleus (cf. estrone Fig. 1). Because of the presence of the 17-keto-group, they are characterized by a color reaction with m-di-nitrobenzene in an alkaline solution (Zimmerman re-

action). This reaction is the basis for a number of relatively simple and acurate methods at present available for the analysis of urinary 17-ketosteroids (229)(230)(231).

In normal subjects under normal environmental conditions, adrenal cortical activity is responsible for two-thirds of the 17-ketosteroid excretion of the male, and for the total 17-ketosteroid excretion of the female. In the male the testis produces the remainder of the 17-ketosteroids. Variations in the amount excreted are in some measure reflections of variations in the amounts of steroids produced by these two glands (232).

There is some confusion as to the exact relationship between the corticoids and 17-ketosteroids. Forbes et al (233), and Venning and Browne (234) have utilized 17-ketosteroid excretion as an index of the androgenic activity of the cortex. The reduction of 17-ketosteroids with stress is taken to mean by them that the androgenic activity of the gland has been reduced and that the cortical hormone has gained precedence to meet the emergency. Sayers (195) on the other hand regards 17-ketosteroids to be degradation end products of the cortical hormone itself. He cites as evidence the parallel increase in 17-ketosteroids, chemocorticoids and biocorticoids after ACTH administration (188)(189)(235), and the increase in 17-ketosteroids (127)(147) following cortisone administration. Further Mason (192) has recently isolated urinary 17-ketosteroids with an oxygen atom on the eleventh carbon, which is a characteristic feature of the structure of the cortical steroids. It is probably true, however, that the activity of the adrenal cortex influences the rate of secretion of 17-ketosteroids, but a number of variables such as sex (231), nutrition

(236) and liver disease (23) may serve to mask or completely obscure the effect of adrenocortical activity.

VI. Regulation of the Rate of Secretion of the Adrenocortical Hormone

(a) Pituitary Regulation of Adrenal Cortical Activity.

Accumulated evidence indicates that the major regulator of adrenal cortical function is the anterior pituitary gland, and that this regulation is achieved through the secretion of adrenocorticotrophic hormone (ACTH). The production of ACTH has definitely been shown to be an essential link in the series of events, intiated by stress, which activates the adrenal cortex.

(1) Hypophysectomy.

Hypophysectomy in the rat results in adrenal cortical atrophy, which can be prevented or corrected by daily homeo-transplants of anterior pituitary substance (47). Stress, which normally increases the size, and decreases the concentration of cholesterol and ascorbic acid of the adrenal cortex, fails to influence the gland in the absence of the pituitary (237), although in the hypophysectomized animal the adrenal continues to secrete minute amounts of the cortical hormone at a steady rate (195).

(2) Administration of the Adrenocorticotrophic Hormone (ACTH).

The adrenocorticotrophic hormone (hereinafter called ACTH) has been isolated as a homogeneous protein from sheep (49) and hog pituitary tissue (50). The hormone so derived is a complex protein substance with a molecular weight of nearly 20,000, and an isoelectric point of approximately 4.7 (49) and capable of stimulating the adrenal cortex

of a hypophysectomized rat. Recently evidence has been presented (238), which suggested that the biological activity of the molecule may reside in a polypeptide fraction of the parent protein, which has been isolated by Li (239).

No substance, other than ACTH, has been observed to have a similar trophic action on the adrenal cortex. In particular no gonadotrophin has been shown to stimulate the adrenal cortex in the absence of the pituitary, except in the special case of the mouse, where a gonadotrophin (luteinizing hormone) apparently acts directly upon the "X" z one (240). Injections of highly purified ACTH, however, will restore the hypophysectomized animal to a state indistinguishable from normal (191), and in man ACTH produces all the metabolic changes which have been attributed to the adrenal cortex.

The major physiological effects of ACTH are dependent on stimulation of the adrenal cortices to produce steroid hormones, the actions of which have been previously described. Administration of ACTH to animals and humans with intact adrenal glands results in increased secretion of glucocorticoids, some of which are closely allied to cortisone, and to a lesser degree in increased secretion of other cortical steroids such as those which influence electrolyte metabolism, and those which have an androgenic function.

In general the administration of ACTH to man (147)(152)(188)(189)(241) and animals (158)(187)(201)(242)(243)(244)(245) produces the following results: it affects carbohydrate and protein metabolism inducing hyperglycemia, glycosuria and a negative nitrogen balance (147)(188)(242)(246); it alters electrolyte metabolism, producing increased

excretion of potassium and decreased excretion of sodium (147)(188) and occasionally sodiumphoresis (188); it inhibits growth in young animals (243) and produces thymic atrophy; it promotes hematologic changes which include falls in total eosinophil and lymphocyte counts (188)(206), an increase in circulating neutrophils and atrophy of the lymph nodes (201); it causes a prompt and pronounced increase in corticosteroid and 17-ketosteroid excretion (189)(235)(246), and enhances the excretion of uric acid. Androgenic effects such as acne and hirsuitism may also follow ACTH administration (147)(188)(189).

Adrenal cortical hypertrophy usually follows the administration of ACTH to animals (247), and the cholesterol and ascorbic acid contents of the adrenal gland are quickly reduced (194)(199)(248)(249). A single dose of ACTH may within three thours result in a 50% decrease in the gland's cholesterol concentration, and it is during this period of cholesterol depletion that evidences of increased cortical hormone activity are observed. This observation suggested, but does not prove, that cholesterol may be utilized in the formation of the steroid hormones (250). The relationship between ascorbic acid and the cortical steroids is not yet established, but the adrenal gland's sensitive response to ACTH with respect to this substance is now used as a means of bio-assaying the potency of ACTH.

(b) Regulation of Pituitary Adrenocorticotrophic Activity.

At present the exact nature of the mechanisms which determine the rate of discharge of the adrenocorticotrophic hormone by the anterior pituitary are not yet certainly known. There are, however, several mechanisms which may be determining factors regulating the production of ACTH.

(1) Peripheral Humoral Mechanism.

The concept of a peripheral humoral mechanism of pituitary regulation considers the acitivy of the adrenal cortex to be dictated by the requirements of the tissue cells of the organism for the cortical hormones (see Fig. 2). That such seems to be the case is suggested by the work of Taylor and co-workers (251), who have been able to demonstrate ACTH in the blood of untreated patients with adrenocortical insufficiency, but not in the blood of normal subjects.

Much evidence has accumulated to support the conclusion that the titre of cortical hormones in the body fluids, which is determined by the requirements of the tissue, regulates the rate of discharge of ACTH from the pituitary. Atrophy of the adrenal cortex has been shown to result from the chronic administration of the adrenal steroids (167) (252), while adrenal hypertrophy, which normally follows application of a variety of non-specific stressing agents such as exercise (237)(253), thyroxin (254) and electroshock (255), has been shown to be inhibited by the administration of DOCA. Further Ingle (237) has shown that cortical extract also will prevent the adrenal hypertrophy which normally follows muscular exercise. The prompt release of ACTH, which normally occurs upon exposure to cold, heat, histamine or epinephrine (210), can be blocked by pretreatment with the cortical hormone (256). Depletion of ascorbic acid, which also normally follows exposure to cold (257) or administration of epinephrine (258), and the lympholytic action of epinephrine (259), can be prevented by the administration of adrenal cortical extract. These many observations suggest that the majority of non-specific stresses stimulate the adrenal cortex to activity by in-

creasing the requirements of the tissue cells for the cortical hormone, which is thereby utilized at a more rapid rate. The elevated titre of cortical hormones produced by administration of adrenal cortical extract or cortical steroids appears to inhibit pituitary adrenocorticotrophic activity, and the resultant adrenal cortical secretory activity, which usually occurs to meet the increased demands for the hormone induced by stressful conditions.

It has been reported that with an increasing intensity of stress, the amount of cortical steroid required to suppress pituitary adrenocortical acitivity becomes correspondingly greater (191)(256). This also may be explained if it is assumed that the rate of discharge of ACTH from the pituitary fluctuates in accordance with the varying requirements of the tissues for the cortical hormone. One may think of the pituitary adrenocortical system as maintaining the tissues in a state of well being with regard to the cortical hormones (eucorticism) under optimal or stressful conditions, just as the pituitary-thyroid system maintains the tissue in a state of well being with regard to thyroxine.

In hypophysectomized animals the trophic action of administered ACTH on the adrenals, as measured by the increased weight of the gland (167)(252) and ascorbic acid deplétion (256), is not influenced by adrenal cortical extract administration. This data has been assumed by Sayers (195) to show that the cortical hormone acts to inhibit the release of ACTH from the pituitary rather than to interfere with the action of the trophin itself on the adrenal cortex.

The operation of the peripheral humoral mechanism as outlined by Sayers (195) suggests that under ideal environmental conditions the

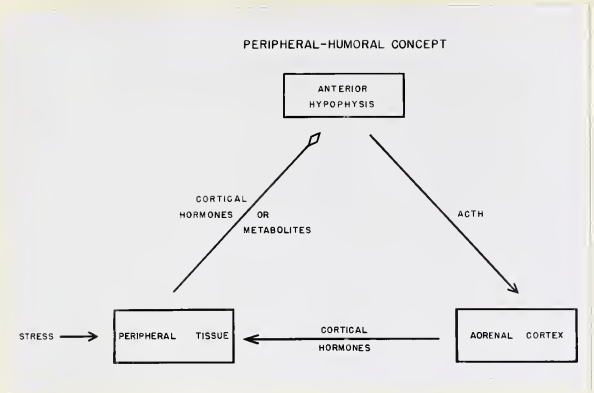


Figure 2.
The Peripheral-Humoral Concept

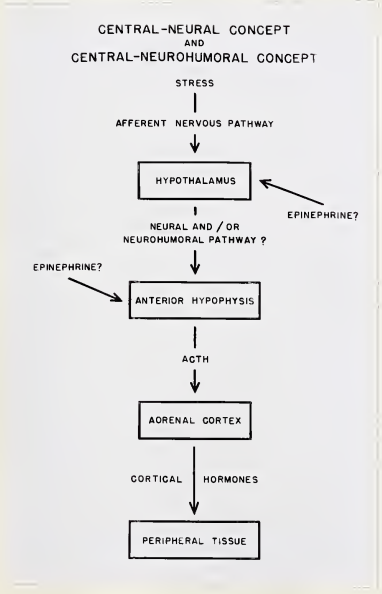


Figure 3.
The Central-Neural and Central-Neurohumoral Concepts.

pituitary adrenocortical system is relatively quiescent. The peripheral tissue cells under these conditions require relatively small amounts of the cortical hormone and the concentration of the latter in the venous blood is maintained at a level which holds the anterior pituitary in check (see Fig. 2. Note the boxed arrow indicating inhibition of the pituitary). Minimum amounts of ACTH are elaborated by the anterior pituitary and minimal amounts of the cortical hormones are secreted by the adrenal cortex.

In contrast the pituitary adrenocortical system is very active under conditions of stress (195)(216)(233)(237)(253)(256). The rate of utilization of the cortical hormone by the tissue cells is increased (191)(256), and hence the quantity in the venous blood is temporarily reduced. The pituitary responds to the reduced titre of cortical steroids (Fg. 2) by discharging ACTH at an accelerated rate. Increased secretory activity of the adrenal cortex follows, by means of which the increased needs of the peripheral tissue for the cortical hormone are met. Sayers (195) further postulates that such increased activity of the pituitary adrenocortical system continues until the stress is removed, or until adaptation occurs, at which time the requirements of the peripheral tissue for cortical hormones is diminished.

The possibility exists that the cortical hormone may act directly on the pituitary or indirectly through some metabolite (see Fig. 2) which varies in concentration as a result of an excess or a deficiency of the hormone. Sayers and Sayers (256) have suggested as a working hypothesis that the action of the cortical hormones is a direct one, because both Cortisone and DOCA inhibit pituitary adreno-

corticotrophic activity in stress despite their quantitatively different metabolic actions (210)(237)(253)(254)(257)(258)(259).

Many apparently anomalous reports on the effect of DOCA administration on carbohydrate metabolism may be explained on the basis of this working hypothesis. DOCA when administered for long periods has been shown to impair the ability of the rat to mobilize glucose when the animal is subjected to a variety of non-specific types of stress (253). DOCA also has been reported to increase the glucose tolerance of alloxan diabetic dogs and rabbits, and of normal and diabetic patients (260), and has been shown to inhibit the hyperglycemic action of epinephrine (261). Cheng and Sayers (262) have demonstrated that chronic DOCA administration induces a state of insulin hypersensitivity, and Woodbury and co-workers (255) have shown that the elevation in plasma sodium and the reduction in central nervous system excitability, which accompany treatment with DOCA, may be restored to normal by the simultaneous administration of ACTH or adrenal cortical extract (ACE).

This data suggests that DOCA induces a metabolic derangement characteristic of a deficiency of the "S" hormones. Part of the action may result from the suppression of pituitary adrenocorticotrophic activity, and thereby the secretory activity of the adrenal cortex, which results in a hormone imbalance characterized by an excess of the administered hormone (DOCA), and a deficiency of the endogenously secreted hormones which influence carbohydrate metabolism. However, the possibility that DOCA and the 11, 17-oxy-steroids ("S" hormones) compete for loci in effector cells must also be considered. Indeed evidence favoring this concept has been recently presented by Woodbury et al (255)

(263), who reported that cortisone and ACE lowered the previously elevated electro-seizure thresholds in adrenalectomized, DOCA implanted animals and suggested that this was due to the competitive action of cortisone and ACE against DOCA for strategic loci in target cells.

The peripheral humoral mechanism of regulatory control, contrary to Selye (51), who postulates hypercorticism as the cause of the pathology of stress, implies that a normal pituitary-adrenocortical system does not allow an organism to be subjected to a plethora of the cortical hormone. Just as a normal pancreas regulates the blood sugar level within a narrow but definite range, so the pituitary adrenocortical system probably maintains "eucorticism", not at a fixed level but at a narrow range of cortical hormone concentrations in the blood. This mechanism is apparently not the only mechanism governing ACTH production by the pituitary for both a central-neural, or neuro-humoral mechanism, and a sympatho-adrenal mechanism seem also to be intimately related to its control.

(2) Central-Neural, or Central Nuero-Humoral Mechanism.

The rapidity with which ACTH is released in response to stress suggests the possibility that a nural or neuro-humeral factor is involved in its release. Cheng and co-workers (264) have demonstrated that section of the pituitary stock in rats does not prevent the discharge of ACTH which usually occurs following injections of histamine, and they concluded that the response to stress is not dependent upon intact neural connections between the hypothalamus and the anterior pituitary. Section of the infundibulum has been reported to have no effect upon the release of ACTH induced by chronic exposure to cold (265). Furthermore

in response to acute stress, ACTH is discharged from pituitary transplants in the anterior chamber of the eye or the spleen (266). Although the degree of ascorbic acid depletion following stress is less in the "transplanted" animals than in intact animals, such data indicates that the integrity of neural or neuro-vascular links between the anterior pituitary and the hypothalamus are not essential for the discharge of ACTH.

Recently Hume (267) reported that although disruption of neural and vascular connections between the hypothalamus and the pituitary in dogs fails to interfere with the function of the pituitary adrenocortical system as measured by the eosinophil test (212), certain specific anterior hypothalamic lesions completely prevent any fall in eosinophils following administration of large doses of epinephrine subcutaneously. He suggests that the hypothalamus releases a neuro-humor[illegible] (see Fig. 3) when activated by stress, for the injection of an acetone extract of the anterior hypothalamus of cattle into animals bearing hypothalamic lesions, resulted in a prompt eosinopenia following the use of epinephrine (267) as a stressing agent.

The central neural and central neuro-humoral mechanisms are essentially similar in that they both attempt to account for ACTH production without regard to the tissue needs for the cortical hormone. Assuming these mechanisms to be the only ones controlling pituitary adrenocorticotrophic activity , the central nervous system in stress would be activated in some way, perhaps through afferent nervous pathways or the direct action of epinephrine on the hypothalamus or the pituitary, or both, and resulting in stimulation of the adrenal cortex. These

mechanisms differ only in that the Central-Neural Concept (see Fig.3) regards the infundibular neural connections between the hypothalamus and the pituitary as being the important link between these structures. Evidence recently presented (267) seems to indicate that the hypothalamus has a secretory function, and that a neuro-humor here elaborated acts on the pituitary causing it to produce ACTH. That epinephrine may act to stimulate these central structures suggests that perhaps the sympatho-adrenal system is essential to pituitary adrenocorticotrophic regulation.

(3) The Role of the Sympatho-Adrenal System.

The close anatomical approximation of the adrenal medulla and the cortex together with the fact that they both play important roles in homeostasis (195) has led to much experimentation regarding a possible relationship between the sympatho-adrenal and pituitary-adrenocortical systems.

In 1908 Babes and Jonescu (268) observed that conditions of stress and multiple injections of epinephrine into rabbits produced a depletion of the supra-renal lipids accompanied by adrenal hypertrophy. Vogt (269) later concluded that epinephrine had a direct stimulatory action upon the adrenal cortex, for she was able to detect cortical hormones in adrenal venous blood of cats and dogs following the administration of epinephrine. Her experiments, however, did not rule out the possibility that the epinephrine had acted through the pituitary and had stimulated the release of ACTH therefrom.

For a time evidence favoring Vogt's direct action thesis was forthcoming. Epinephrine was shown to produce a lymphocytopenia in the

hypophysectomized rat (270) and an eosinopenia in the hypophysectomized mouse (271). On the other hand only ACTH, and not epinephrine, was shown to stimulate the production of chemocorticoids by the isolated perfused adrenal gland (272).

Sayers (195) suggests the following possible mechanisms for the action of epinephrine in inducing the discharge of ACTH from the anterior pituitary: I. epinephrine may act centrally on effector cells in the adenohypophysis or through the hypothalamus which in turn would activate the anterior pituitary; II. epinephrine may act like other non-specific agents and stresses to increase tissue utilization of the cortical hormone with a consequent lowering of the venous titre of the hormone (Fig. 2 & 4); III. epinephrine may be the denominator common to all types of stress and the specific agent which promotes utilization of the cortical hormone by the tissues (Fig. 4); IV. epiphrine may act by any one of the various possible combinations of these three (see Fig. 5).

In a recent review of the subject Sayers (195) points out that if epinephrine acts centrally (cf. Fig. 3) to bring about discharge of ACTH without regard to the rate of utilization of cortical hormone by the tissues, or to the titre of the hormone in venous blood, it follows that epinephrine should be therapeutically beneficial. If on the other hand epinephrine acts by increasing cortical hormone utilization by the tissues (fig. 2), then it would be expected to be of slight benefit at most for the tissue instead of being flooded with an excess of cortical hormone will receive only quantities of hormone appropriate to the increased needs induced by epinephrine. Further he suggests that the

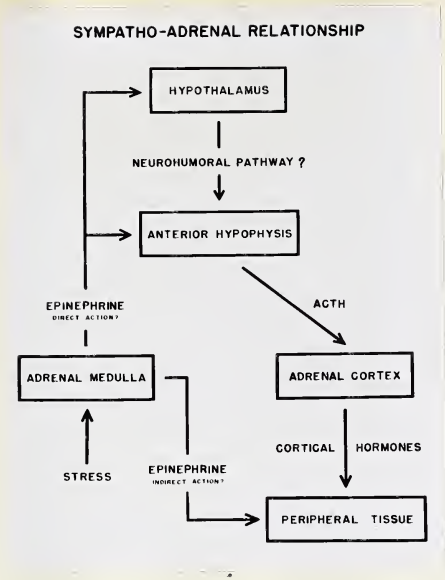


Figure 4
Sympatho-Adrenal Relationship

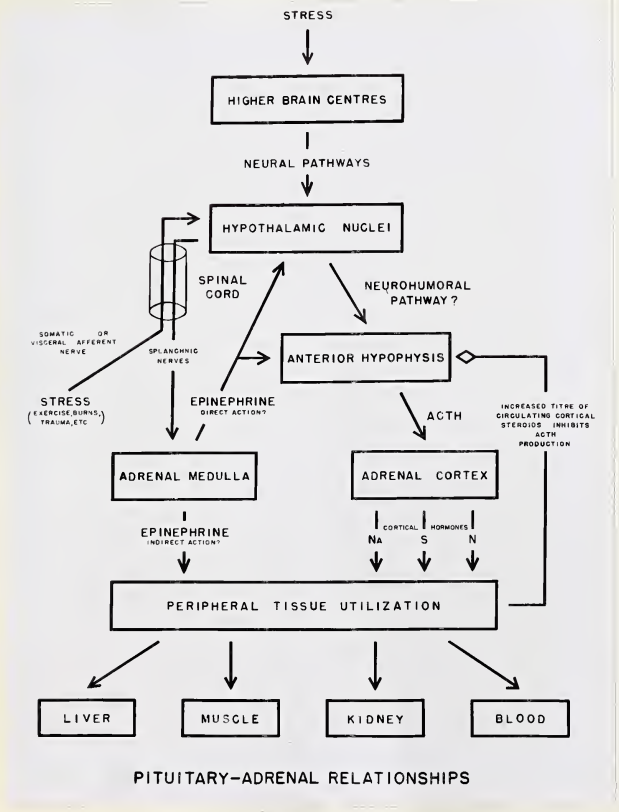


Figure 5.
Pituitary-Adrenal Relationships.

elevation of the titre of the cortical hormone in arterial blood necessary to meet the increased tissue requirements, may be expected to have some influence upon the diseased tissues. Interestingly enough Thorn and co-workers (152) reported a slight but definite improvement in rheumatoid arthritis following epinephrine administration, although the effect was significantly less than that obtained with ACTH. In explaining this result Thorn and associates state that "In contrast to the uninhibited stimulation of the adrenal cortex that follows the repeated administration of ACTH, epinephrine administration has the disadvantage of losing much of its effectiveness as an adrenal cortical stimulator, since endogenous ACTH production is inhibited by a rising titre of adrenal cortical steroids."

Several workers (191)(258) have shown that in the intact animal, reduction in adrenal ascorbic acid and the lymphocytopenic action (259) produced by epinephrine can be prevented by prior administration of the cortical steroids. Further neither dibenamine, an agent which blocks the excitatory effects of both sympathin and epinephrine (273), nor tetramethylammonium bromide, an autonomic ganglionic blocking agent (274) influences the reduction of adrenal ascorbic acid, which takes place in the rate in response to acute stress. These observations suggest that epinephrine acts like other non-specific stresses by increasing tissue utilization of the cortical hormone, and that it has no direct action upon the pituitary.

However Long (257)(258) regards epinephrine as an unusual type of non-specific stressing agent. He suggests that epinephrine is the major factor in the activation of the adrenocorticotrophic secretion

from the anterior lobe of the pituitary, but that it is further regulated by the blood level of the cortical hormones.

It has been pointed out that epinephrine may be the common denominator to all types of stress. Evidence on this point is meagre and is conflicting. The completely sympathectomized dog is hypersensitive to insulin, but resists cold, heat and anoxia almost as well as do intact control animals (275). This would suggest that acceleration of adrenocortical activity in response to acute stress is not dependent upon the activity of the sympatho-adrenal system. However, it appears that epinephrine is not essential for the acion of the adrenocortical hormone on the tissues, for the addition of epinephrine to an infusion of ACE did not improve muscular work performance of adrenalectomized rats over that of similar animals given ACE alone (276). Although the sympatho-adrenal system apparently is not essential for the response of muscle cells to cortical extracts, the integrity of the pituitary adrenocortical system appears to have considerable influence upon the responses of certain specific effector cells to epinephrine. For example, the pressor response to sympathetic stimulation is diminished by adrenalectomy and restored to normal by cortical steroid replacement therapy (277). It would seem in the light of present investigation that the sympatho-adrenal system actively drives organs and organ systems to increased functional activity in emergenices, whereas the pituitary-adrenocortical system plays but a passive role by making cortical hormones available in quantities appropriate for the varying needs of the organism. In more simple terms, the sympatho-adrenal system appears to initiate, whereas the pituitary-adrenocortical sytem appears to support cellular activities.

VII. Some Physiological Changes Occuring in Stress.

Since Selye (51) first presented his concept of the General Adaptation Syndrome much work has been done to determine the relationship of the adrenal cortex to stress. That such a relationship exists is strikingly revealed when one compares the metabolic effects of stress with the effects of cortisone and ACTH administration previously described.

(a) Increased Utilization of the Cortical Hormone.

Hyperactivity of the adrenal cortex comparable with that observed following ACTH administration and an increased rate of utilization of the cortical hormone is necessary for the mobilization of energy for cellular work, because it has been shown that the adrenal cortex is hypoactive in myxedema (278) and hyperactive in hyperthyroidism (279) (254)(278), in which state all cellular activity is markedly accelerated. These facts would suggest that the increased rate of cortical hormone utilization parallels the increased cellular activity occuring during stress. Such a parallel relationship also would account for the inability of cells in adrenal insufficiency to perform functions which require a relatively great expenditure of energy (280)(281).

(b) Metabolic Changes.

(1) Carbohydrate, Protein and Fat Metabolism.

Trauma in man irrespective of its locus is followed commonly by glycosuria and a reduced tolerance to glucose (282). Anoxia has been shown to reduce the glucose tolerance of the dog (283) and to elevate the urinary nitrogen (284). Intact animals (285)(286) and patients with normal function of the pituitary-adrenocortical system character-

istically show an increased rate of excretion of nitrogen after trauma. On the other hand following adrenalectomy, trauma (285)(286) in the rat, or anoxia in the dog fails to elevate the urinary nitrogen. Fat is mobilized and stored in the liver of the mouse following exposure to stresses such as cold and strenuous exercise (287). Experiments of this nature have been interpreted to mean that the adrenal cortex is largely responsible for the diabetic-like state and the catabolism of protoplasm which accompanies stress in the form of injury, since the cortical hormone characteristically acts to inhibit glucose utilization (151)(158)(160), increase protein catabolism and urinary nitrogen excretion (154)(155), and to increase the storage of fat (287).

Recent experimental data would seem to indicate, however, that the adrenal cortex plays a supportive role rather than a causal role in the phenomena cited above. The hyperglycemic reaction fails to occur in the absence of the adrenals, but a dose of ACE, which does not elevate the blood sugar of non-traumatized normal rats, restores the hyperglycemia of trauma in adrenalectomized animals (288). Similarly it has been demonstrated that amounts of ACE, which did not cause an increase in urinary nitrogen excretion in an untraumatized normal rat, make it possible for adrenalectomized animals to excrete nitrogen at a rate comparable with that of intact rats in response to equal degrees of trauma (286).

(2) Electrolyte Metabolism.

A number of stresses such as hemorrhagic shock, muscle crush, surgery and intestinal obstruction produce a characteristic feature of adrenocortical insufficiency, in that there is an accumulation of potassium in the extracellular fluids, and an increased urinary excretion of

that element (195). The accelerated excretion of potassium is thought to be mediated by the adrenal cortex for cortisone characteristically results in an increased urinary excretion of potassium and chlorides (52)(147).

It is very difficult to establish whether the adrenal cortex plays a causal or supporting role in the production of the electrolyte metabolic changes observed in stress, as there are numerous other factors which influence electrolyte metabolism.

For example, it previously has been pointed out that DOCA administration results in sodium retention (134). Recently, however, it has been shown that the elevation of plasma sodium produced by DOCA in rats can be prevented by the simultaneous administration of ACTH or ACE (255). This coupled with the fact that cortisone (an "S" hormone) has been reported to induce sodium retention in an Addisonian patient (126) has prompted Woodbury et al (255) to conclude that the "S" hormone can normalize plasma sodium regardless of the direction from normal, whereas DOCA acts always to produce sodium retention. Such observations serve to mask the precise role of the adrenal cortex in the production of the electrolyte changes observed in stress.

The marked similarity of the metabolic effects of stress and those produced by the administration of cortisone suggests that the adrenal cortex determines the response of the organism to stress. It follows that resistance to stress, although a complex phenomenon, may be also intimately associated with adrenal cortical function.

VIII. Resistance to Stress.

(a) Definition.

The term resistance to stress is defined by Sayers (195) as that capacity of the organism to maintain constancy of the internal environment, and normality of body functions during exposure to stress. The degree of resistance to stress may be measured in a number of ways, including mortality, maintenance of normal concentrations of metabolites in the body fluids, and the maintenance of body functions.

It has been firmly established that resistance to stress after adrenalectomy is markedly decreased and that the adrenalectomized animal is extremely sensitive to a great variety of agents and environmental changes (69)(70)(71)(72)(73). This fact suggests that resistance is a function of the adrenal cortex and particularly that lowered resistance may be due to a hypocorticism produced by stress.

(b) Mechanisms Producing Hypocorticism.

Several mechanisms which may produce hypocorticism have been suggested, among which are:

(1) An Inadequate Pituitary-Adrenocortical System.

If the adrenocortical system was incapable of producing hormones in sufficient quantities to meet the increased demands of the tissue during stress, it should follow that steroid therapy would increase the resistance of the intact animal to stress. However, administration of neither DOCA or ACE increases the survival rate of intact mice (289), or rats (290) from scalds, or infection with B. Tularense (291). Although Kottke et al (292) have shown that Kendall's extract will increase the resistance of intact mice to hypoxia, the general im-

pression one gains from a recent review by Swingle and Remington (293) is that cortical steroid therapy is of no benefit in improving the resistance in the intact animal.

(2) Exhaustion of the Adrenal Cortex.

Various bacterial toxins produce hyperemia, hemorrhage and necrosis of the adrenal cortex of the rabbit (294) and the guinea pig (295). Sayers (195) postulates that such toxins may impair the cells of the adrenal cortex and that a relative state of insufficiency of the cortical hormone may be so induced, but he condems the use of the descriptive term "exhaustion". He states that the conclusion that a gland exhausted of its precursors is impaired in its secretory activity, is not justified in the light of present knowledge regarding the relation of the concentration of certain constituents to glandular secretory activity.

(3) Exhaustion of the Pituitary.

The possibility that a deficiency of the secretory activity of the adrenal cortex may arise as a result of deficient production of ACTH must also be considered. Because ACTH is a protein, a deficiency of amino acids may limit the production of the hormone. In this regard it has been demonstrated that the rate of excretion of biocorticoids by debiliated individuals subjected to an acute traumatic event increases slightly or not at all (234), which suggests that the adrenal cortex is less active in mal-nourished than in normal subjects in stressful situations. Sayers (195) however, reports that despite the prolonged discharge of ACTH in scald cases, the pituitary content of ACTH is depleted not more than 50 percent of normal. This observation

strongly suggests that the rate of discharge of ACTH is never the limiting factor in the ability of the pituitary-adrenocortical system of the normal organism to meet the production requirements of an emergency.

It has been inferred from this data (195) that the survival of an organism with intact adrenals from an exposure to a stress, which severely taxes its resistive capacity, is not limited by the failure of the adrenal cortex to fulfill the tissue needs for the cortical hormone. Apparently the answer to the problem is not concerned primarily with the supply of the cortical hormone, but rather with the action of the hormone.

IX. The Mode of Action of the Cortical Hormone in Increasing Resistance to Stress.

The markedly increased sensitivity to stress occasioned in the adrenalectomized animal (69)(70)(71)(72)(73) has caused considerable speculation as to the mechanism by means of which the adrenal cortex confers resistance. Several possible mechanisms have been suggested by various workers in the field.

(a) The Detoxification Theory.

Arising from the detoxification theory of Brown Sequard (296) is the belief that the resistance of the animal to stress is related to the action of the cortical hormones in detoxifying noxious agents released from injured or metabolically deranged tissues. Histamine has been indicated as the endogenous toxic agent, and the adrenalectomized animal has been shown to have less than normal ability to inactivate histamine, which ability can be restored to normal with DOCA or ACE

therapy (297). Also both blood (298) and tissue (299) histamine levels have been reported to be elevated following adrenalectomy presumably because histamine is inactivated less readily in the adrenalectomized animal than in the intact animal (297).

(b) Cardiovascular Theory.

Swingle and Remington (293) have reviewed the evidence regarding the influence of the cortical hormone upon the cardiovascular system and concluded that although alterations in the vascular dynamics contribute significantly to the collapse of the adrenocortical insufficient animal, they are not the major cause of the increased susceptability of the adrenalectomized animal to various stresses.

(c) Antibody Mobilization Theory.

According to White and Dougherty (300) the lymphocytes contain a portion of the globulin fraction of serum, the rate of release of which is under the control of ACTH and the adrenal cortex. They have presented evidence that an adrenal cortical regulation of antibodies offers an explanation for the elevated antibody titre which occurs in response to a large number of non-specific stresses (301). Contrary to this concept, other workers have found that adrenalectomized rabbits produce antibodies in excess of the amount produced by intact animals (302), and animals treated with ACTH did not produce increased amounts of gamma globulin (303). The action of the adrenal cortex in increasing the resistance of the organism to infections and toxins is apparently dependent in small measure at most upon the release of antibodies from lymphocytes (195).

(d) Ubiquity Theory.

Gordon and Katsh (304) have recently reported that the adrenal cortex exerts an influence upon the phagocytic capacity of the reticulo-endothelial system. Sayers (195) suggests that this may be the mechanism by means of which the adrenal cortex increases resistance. Further he predicts that all paths of investigation into this particular phase of adrenal physiology will ultimately converge upon the conclusion that it is the ubiquitous role of the cortical hormone in the function of the body which holds the key to the increased resistance to every kind of stress. He states "that it is not unlikely that the varied actions which have been assigned to the adrenal cortex are manifestations of a single fundamental role of the hormone in an enzatic process common to all cells."

X. Adaptation to Stress.

(a) Definitions.

Adaptation may be defined as that state of the organism characterized by increased resistance to stress, wherein previous continued or intermittent exposure to stress has induced changes which enable the organism more efficiently to counteract potential or actual alterations during subsequent exposure to stress. Selye (51) defines the sum of all these non-specific systemic changes brought about by long continued exposure to stress as the General Adaptation Syndrome. Specific or non-crossed adaptation is adaptation acquired through repeated exposure to the same agent, whereas non-specific or crossed adaptation is adaptation to a particular stress acquired through exposure to a different stress. The development of antibodies to bacteria, and the

increase in the number of circulating red blood cells in response to continued exposure to low barometric pressures, are striking examples of adaptation.

(b) The General Adaptation Syndrome.

Selye (51) has described a pattern of alterations which may occur upon the exposure of an animal to stress under the term "General Adaptation Sydnrome". There are three stages recognized as belonging to this syndrome: the alarm reaction, the stage of resistance, and the stage of exhaustion. The alarm reaction is defined by Selye (51) as the sum of all non-specific systemic phenomena elicited by sudden exposure to stimuli to which the organism is neither quantitatively or qualitatively adapted. Generally speaking the signs of the alarm reaction are those of shock, and include hypothermia, hypotension, tachycardia, hemoconcentration, increased capillary permeability, and nervous depression. If it is mild, however, there may be no shock in the ordinary sense of the word, and slight hyperglycemia, tachycardia and leucocytosis may be the only detectable symptoms. There is a continuous series of transitional steps between the definitely physiological adaptive processes to the stress of every day life, and the most severe alarm reactions which may cause death. Such severe reactions are characterized by extreme tissue catabolism with pancreatic, thymic and lymphatic tissue involution; a lymphopenia and polymorphonuclear leucocytosis; and erosion of the gastrointestinal tract. According to Selye (51) the blood sugar may be elevated initially, after which it falls. The blood Non-protein Nitrogen and serum potassium are elevated and the concentration of blood chlorides

is decreased. Opposed to this so-called "shock phase" is the defensive potion of the alarm reaction called the "counter shock phase" during which there is adrenal cortical enlargement, a progressive increase in corticotrophins and corticoids, and resistance rises to or above normal. It is important to note that during the "shock phase" the adaptation to the alarming agent (specific resistance) is acquired at the expense of resistance to other (non-specific) stresses. During the "counter shock phase" non-specific resistance is increased, but this crossed resistance (non-specific resistance) is never as great as the specific resistance to the particular agent with which the alarm reaction was produced.

The second stage of the General Adaptation Syndrome is called by the author the stage of resistance and is defined as the sum of non-specific systemic reactions to prolonged exposure to stimuli to which the organism has acquired adaptation. During this period the organism has an increased resistance, especially to the stress to which the organism was exposed. Most of the morphological and biochemical changes of the alarm reaction disappear, and in some cases the deviation from the normal is reversed.

Selye (51) denotes the third and final stage of the General Adaptation Syndrome as the stage of exhaustion, which is the sum of all non-specific systemic reactions developing as a result of prolonged exposure to stimuli to which adaptation had been developed, but could no longer be maintained. During this stage adaptation wears out, the lesions of the alarm reaction re-appear, and further resistance becomes impossible.

(c) The Clinical Importance of the General Adptation Syndrome.

The clinical importance of the General Adptation Syndrome has only recently become evident. It was noted that exposure to non-specific damaging agents (e.g. cold) would produce hypertension and nephrosclerosis in animals sensitized by unilateral nephrectomy and a high sodium intake (319). Pituitary extracts and DOCA have also been shown to be active in eliciting such responses, the changes not infrequently being accompanied by widespread periarteritis nodosa with myocardial lesions and arthritis similar to that seen in patients with rheumatic fever. These experimental observations are all compatible with the view "that during the General Adaptation Syndrome certain hormones of the anterior pituitary and the adrenal cortex are produced in excessive amounts in order to increase resistance." This increased production of such hormones is thought by Selye (51) to result in an endogenous hormone intoxication, which causes the appearance of renal, cardiovascular and joint diseases. On this basis Selye developed the concept that the most common maladies of man are "diseases of adaptation", resulting from abnormal adaptive reactions to stress. Among the diseases which Selye considers to have a relation to the General Adaptation Syndrome are nephrosclerosis, hypertension, nephritis, rheumatic fever, rheumatoid arthritis, periarteritis nodosa, eclampsia, gastrointestinal ulcers, the appendicitis not uncommonly associated with a variety of contagious diseases, and the acute tonsilitis which may follow burns or other non-specific injuries.

XI. Does Stress Produce Pathological Changes?

In view of the hyperactivity of the adrenal cortex and increased corticoid production, which is known to occur during stress, there is a possibility that there may be pathological changes which result from stress other than the direct action of the mechanical forces involved. However, the evidence concerning this point is extremely controversial. Selye investigating the toxicity of the adrenal hormones has marshalled much material to support his thesis that chronic endogenous intoxication with the cortical hormone is the primary cause of the "Diseases of Adaptation".

(a) Toxicity of DOCA.

Experimentally Selye and co-workers (51)(305)(306)(307) have produced pathological changes in the heart, blood vessels, kidney, brain and joints following the adminstration of DOCA to rats sensitized by unilateral nephrectomy and a high salt intake. Cardiac lesions similar to those of rheumatic endocarditis, periarteritis nodosa, polyarthritis and nephrosclerosis have been observed in rats so treated. In the chicken (305) DOCA with a normal sodium intake has been observed to induce edema and nephrosclerosis.

Sayers (195) points out that it is difficult to reproduce pathological changes in animals by DOCA administration. Indeed some workers (308) have been unable to reproduce Selye's work and have reported that prolonged daily administration of DOCA did not induce pathological changes in the heart of the rat. Harrison (309) attributes the lesions described by Selye to infection alone or in combination with cold, for he found that rats with pneumonia exposed to cold develop

cardic lesions whether treated with DOCA or not. The impression is gained that DOCA must act in combination with as yet unknown factors in the production of pathological lesions in experimental animals.

(b) Toxicity of ACE and the 11-17-Oxysteroids.

Neither ACE nor the 11, 17-oxysteroids have been shown to produce pathological changes similar to those induced by DOCA. Cortisone has been reported to induce moderate hypertension in intact nephritic rats and striking hypertension in adrenalectomized nephritic rate (310). In Cushing's syhdrome, which according to Albright (123) is caused by the excessive production of the 11, 17-oxysteroids or "S" hormones, there is a high incidence of nephritis and arteriosclerosis in adults (311) and of kidney damage in children (312), but Aschoff nodules, periarteritis nodosa and rheumatoid arthritis apparently do not occur in this syndrome. Selye is aware of these findings and has accordingly (313) ascribed the cause of the "diseases of adaptation" to an excessive or abnormal production of the salt active corticoids in response to non-specific damage.

(c) Toxicity of ACTH and Anterior Pituitary Extracts.

Nephrosclerosis and cardiac lesions have been produced in intact animals by the administration of lyophylized extract of anterior pituitary tissue in conjunction with a high protein diet (314). These experiments were confirmed by Ingle (315), who reached the tentative conclusion that the adrenal cortex is a supportive, but not causative factor in the development of nephrosclerosis, cardiac and joint lesions.

The pituitary powder used by Hall (314) was extremely toxic and in view of this it is interesting to note that Simpson and co-

workers (316) failed to detect any changes in the size or histology of the kidney of rats given a purified preparation of ACTH for both short and long periods of time. No Aschoff nodules, periarteritis nodosa, or increase in heart size were observed in mice treated in a similar manner for as long as 38 weeks (317).

Sayers (195) agrees with Selye (51)(56) that during stress the adrenal cortex is hyperactive, and that the production of the cortical hormones is greater than under optimal conditions. This according to Sayers (195), however, does not mean that the production is excessive enough to permit intoxication, but rather it means that the production of the cortical hormone has been accelerated to meet the increased needs of the tissue. Sayers states "that Selye fails to distinguish between cortical hormone production by the adrenal cortex, and the status of the tissues of the organism in regard to the cortical hormone requirement". He points out that it is possible for the tissues to be in a state of eucorticism, hypercorticism, or hypocorticism with a hyperactive gland depending upon the requirement of the tissue cells for the hormone. Further he doubts that there is sufficient inertia in the pituitary-adrenocortical system to permit hypo or hypercorticism to persist for more than an hour, and that on the whole a state of eucorticism exists.

(d) Deficiency of 11, 17-Oxysteroids Induced by DOCA.

According to Cheng and Sayers (262) DOCA treatment leads to a state of hormone imbalance characterized by an excess of DOCA and a deficiency of the 11, 17-oxysteroids ("S" hormones). This state of hormone imbalance must also be considered as a possible basis for the pathology seen in the cardiovascular system. The pathology so induced

may be the result of a lowered resistance due to the deficiency of the "S" hormone. In confirmity with this hypothesis Woodbury et al (318) have shown that the administration of ACTH inhibits the development of pathological changes induced by DOCA alone.

(e) Production of the Diseases of Adptation.

Selye (319) produced hypertension and nephrosclerosis in rats sensitized by unilateral nephrectomy and a high sodium diet by subjecting them to cold, formalin and vigorous exercise. However, he reported finding no Aschoff nodules, periarteritis nodosa or arthritic changes. It would appear from these studies that cold, formalin and exercise alone or in combination with a high salt intake do not reproduce the changes induced by DOCA. Selye has not as yet presented convincing evidence that chronic exposure of animals to stress uncomplicated by DOCA administration induces pathological changes characteristic of the collagen diseases.

XII. Therapy of Collagen Diseases with Cortisone and ACTH.

The recent successful use of cortisone and ACTH in the treatment of the collagen diseases has not as yet been properly explained. The findings are not compatible with the thesis that the collagen diseases are induced by hyperactivity of the adrenal cortex preferentially or otherwise. A number of theories have been postulated to explain the therapeutic action of ACTH and cortisone. Among those which have appeared as the following:

(a) Interference with the release of, or the toxic action of, anaphylacogenic substances resulting from the antigen antibody reaction (320).

(b) Alterations of cell permeability through hyaluronidase (321).

(c) Suppression of mesenchymal tissue, and in particular the inhibition of the development of granulation tissue (322).

(d) Maintenance of eucorticism in a deficient connective tissue characteristic of the collagen diseases, which connective tissue may be abnormally insensitive to the cortical hormone (195). In this concept the deficiency is not in the adrenal or the pituitary, but in the peripheral tissue itself, and restoration of eucorticism may be accomplished only at the price of hypercorticism in the cells with normal sensitivity to the cortical hormone.

However, much more work is required to determine if any of these hypotheses actually account for the therapeutic effects of cortisone and ACTH in the treatment of the collagen diseases.

C. Introduction to the Problem.

Throughout the literature pertaining to the adrenal cortex and the cortical hormones many controversies are noted, all of which will require extensive clinical investigation for final clarification. Data obtained from animal studies are not enough upon which to make conclusions with respect to man, for species differences are always a problem complicating the interpretation of such results. Ultimately the knowledge obtained from animal research must be confirmed by clinical investigation.

With this in mind, and to provide further data which may aid in the solution of the complex problem pattern surrounding the adrenal cortex, a series of clinical projects were undertaken with the co-operation of selected patients. The precise nature of the studies was de-

termined by the availability of ACTH and cortisone, the laboratory and hospital facilities at our disposal, and the clinical material which was in the hospital during the time allotted for this work. We were indeed fortunate in being able to study patients with Cushing's syndrome, Adrenogenital syndrome, Allergic Urticaria and Epilepsy.

D. Methods.

(I) Hospitalization.

All subjects were hospitalized on a metabolic ward permitting close supervision of diet, fluid intake, activity and the collection of the necessary specimens. They were ambulatory and moderately active in the ward.

(II) Diet.

During the experimental period the proportions of fat, carbohydrate and protein in the diets were as uniform as possible. Caloric intakes were adjusted to meet the needs of the individual patient. Mrs. C. and Miss C. W. received 1900 calories daily, except for days one to three when they received 2200 calories; Mrs. J. W. also received 1900 calories daily; Mr. R. C. received 1700 calories except for days one to three when he received 1500 calories per day; and Mr. M. A. received 2000 calories per day. The dietary intake of sodium, potassium, chlorine and nitrogen was calculated daily using standard tables (323)(324).

(III) Fluid Intake.

Fluid intake was not accurately measured except in the case of Mr. M. A. During the initial course of investigation and the first nine days of the second investigation period, water was permitted ad

libitum and thereafter was restricted to 700 c.c. a day. The preformed water of the food and the water of oxidation obtained from standard tables (324)(325) were also considered in the calculation of the total fluid intake in this case.

IV. Collection of Specimens.

(a) Urine.

Urine collections, without preservative, were made for 24 hour periods, and daily creatinine determinations were done as a check against incomplete collections. After the collections were completed, the volume and specific gravity were recorded and they were stored at ice-box temperature until a three day pool# had been amassed, when suitable aliquots were taken for analysis. Samples of each three day urine pool and all unused serum specimens were frozen for future checks. All glass containers used were washed without soap in tap water, and then in distilled water to prevent contamination of the specimens.

(b) Blood.

Fasting blood for the determination of circulating eosinophils, serum sodium, potassium and chlorides, and CO_2 combining power was drawn on the second day of each three day pool. In the case of Mrs. C. and Miss C. W. additional blood was also drawn at this time for total protein and fasting blood sugar determinations. Serum studies were not done in the case of Mrs. J. W. Blood for the determination of potassium and sodium was drawn without an anti-coagulant into syringes washed without soap and rinsed in distilled water, and then in sodium free water. It was allowed to clot in tubes treated in a similar manner, immediately after which the serum was separated by centriguation. Blood

In some instances two or four day pools were used.

for the hematological studies was preserved in balanced oxalate. White blood counts, differential counts, hemoglobin determinations and hematocrit studies were done by routine methods. Eosinophil counts were performed using the method described by Randolf (326)(327).

V. Blood Pressure and Weight Determinations.

Blood pressure determinations were carried out on all patients three times daily by the same observer and using the same sphygmomanometer. Each patient was weighed once daily on the same scales with an empty bladder, and just before the noon meal. The stool was not retained for examination.#

VI. Chemical Methods.

The following chemical methods were employed:

Urine creatinine was determined by the method of Folin as modified by Bosnes and Taussky (328), and urinary nitrogen by the micro-Kjeldahl method (329). Urinary and serum chlorides were determined by the Harvey modification (330) of the Volhard-Arnold method (331), and the method of Schales and Schales (332) respectively. Plasma CO_2 combining power was determined by the method of Van Slyke and Cullen (333), and total plasma proteins by the Biuret method (334). Fasting Blood sugar determinations were performed using a modified micro-Shaffer-Hartmann method (335). Duplicate sodium and potassium determinations were performed on both urine and serum specimens using Beckman and Barclay flame photometers (336)(337) (see Appendix 1).

The determination of urinary formaldehydogenic steroids; i.e. "Cortin", (see Appendix 2), was performed by the method of Daughaday, Jaffe and Williams (227) as modified by Venning. Partitioning between

Except in the case of Mr. M. A.

benzene and water for separation of the desoxysteroids and the 11-oxysteroids was retained because it also assists in preventing artifacts, which may be introduced from contaminants in the redistilled chloroform. No back extraction was performed on the 0.2 N. and 0.1 N. sodium hydroxide washes, which were used to remove most of the pigments and other non-corticoid material present in the chloroform extract. Normal values by this method generally range from 0.5 - 1.5 mgms. per day under basal conditions.

Measurements of 17-ketosteroids were made using the method of Holtorff and Koch (229). Ketonic separations were not performed, and only partial correction for non-ketonic chromagens was attempted using a potassium hydroxide blank.

VII. Statistical Methods.

Statistical treatment of the data was performed using the methods described by Walker (338).

E. Case Reports and Results.

I. Cushing's Syndrome Treated with Cortisone.

(a) Introduction.

According to Albright (123) Cushing's Syndrome is a form of hyperadrenocorticism which may result from a pituitary basophil adenoma (Cushing's Disease), or from some hyperplastic or neoplastic dondition of the adrenal cortex itself. In many respects the disorder is the direct opposite of another syndrome associated with hyperactive adrenal cortex, namely the adrenogenital syndrome. The former condition is characterized by a cessation of growth before epiphyseal closure and a

decrease in strength, muscle mass and skin thickness, whereas the latter disorder is characterized by a tendency towards masculinity, rapid growth before epiphyseal closure, and increased strength, muscle mass and thickness of skin.

From the endocrine point of view Albright (123) attributes the manifestations of Cushing's syndrome to an excessive production of the "S" hormones (11, 17-oxysteroids) by the adrenal cortex. That such is the case has been substantiated by Mason et al (339), who isolated 17-hydroxycorticosterone (an "S" hormone not normally found in urine) from the urine of a patient having Cushing's syndrome. In addition it is well known that in subjects with normal adrenal glands, high dosage schedules of cortisone (also an "S" hormone) and ACTH maintained for a long time will produce the characteristic features of Cushing's syndrome, which will disappear on cessation of therapy (147)(188).

The clinical features (153)(340) which usually appear in this syndrome are: a mild diabetes which is resistant to insulin; a pronounced muscular weakness with a low creatinine excretion indicating a descreased muscle mass; and osteoporosis, which is most frequently observed in the spine and often associated with nephrolithiasis. There is a peculiar obesity of the face ("moon face"), neck and trunk, whereas the extremities are thin and may even be wasted. The thin atrophic skin covering the thighs and the abdomen is easily bruised and is often marked with wide purplish striations. Mild hirsuitism without other evidences of masculinity, amenorrhea, impotence and diminished libido may also be observed. A mild erythrocytosis and hypertension may occur, but the urinary excretion of cortin-like substances (11-oxysteroids) always is increased significantly.

Patients with Cushing's syndrome have been reported to respond in a normal manner to ACTH administration (341)(342), although ACTH is known to increase "S" hormone production by the adrenal cortex. The manner in which such patients respond to cortisone has not been thoroughly studied, and as opportunities do not often arise to conduct metabolic studies on patients having the disease, we were fortunate to be able to determine the metabolic effects of cortisone in this instance. The results obtained proved interesting, particularly when compared with those from a similar study done at the same time on a patient with the adrenogenital syndrome.

(b) Case History #96690.

The patient, Mrs. C., a 38 year old female, apparently was well until four years prior to admission, at which time she noticed that her eyes had suddenly become "bloodshot and puffed up". She was treated at this time for an infection and possible allergy. A series of allergy tests revealed no specific allergin, but physical examination revealed an elevated blood pressure and she was accordingly placed on a salt free diet. Her eye symptoms remained unchanged and she developed pains in the back of the neck and weakness, for which she was hospitalized with no improvement. Two years prior to the present admission a diagnosis of hyperadrenocorticism was made by Dr. D. R. Wilson, and testosterone proprionate 10 mgm. per day was prescribed. Eight months prior to admission she commenced to menstruate and has maintained normal frequency, although the flow is scanty. Four months later the patient was seen by Dr. J. S. L. Browne of Montreal, who raised her testosterone dosage to 20 mgms. per day. Since beginning testosterone therapy she has noted an

Figure 6.

Cushing's Syndrome #96690. Photograph showing slight puffiness suggestive of moon face.

increase in her strength, some diminution in the tendency to bruise, and states that her face is "less round than before". Three months prior to this investigation testosterone proprionate was discontinued.

On physical examination the patient weighed 60 kgms. Moderate hirsuitism was apparent on the forearms, legs and thighs, and was slight on the chin and cheeks. Some puffiness of the face was noted, which was suggestive of the characteristic "moon face" (Fig. 6) and her skin was thin and reddish and bruised easily. Her blood pressure on admission was 140/95. There was no enlargement of the heart to percussion, and no murmurs were heard. Ophthalmoscopic examination revealed no hemorrhages or exudates and there was questionable A. V. nicking. Decreased motor power was noted in both quadriceps, and the right grip was weaker than the left. All reflexes were normal.

Routine urinalysis and her hemogram were within normal limits. An intravenous pyelogram showed the kidneys to be normal in size, shape and position, and the right kidney was noted to have a bifid pelvis. A lateral x-ray of the lumbar vertebra showed slight osteoarthritic lipping, but no osteporosis. No chest x-ray was done, and perirenal insufflation was not attempted in this or any other of the reported cases, as we have had no experience in the procedure. A cortin determination on admission was 1.6 mgm. per 24 hours.

(c) Procedure.

Prior to instituting therapy a six day control period was carried out. Cortisone, 200 mgm. q.d., was administered intramuscularly for the next six days, following which it was discontinued and the patient was observed for a period of twelve days. Following her discharge the

patient visited the Mayo Foundation where an adrenal tumor was removed.

(d) Results.

(I) The Effects of Cortisone on Electrolyte Metabolism

(See Figs. 7 and 8).

a. Sodium Balance.

During the first three days of the control period the patient was in sodium balance, while during the remainder of the control there was a slight retention of the element. Cortisone, 200 mgm. daily, resulted in a slight diuresis of sodium during the first three day period, which was followed by a slightly positive balance. On cessation of treatment there was a diuresis of sodium after which balance was restored.

Serum sodium values showed some elevation during the administration of cortisone, but these values remained within normal limits.

b. Chloride Balance.

The urinary chloride balance closely followed the sodium balance. Cortisone produced a slightly negative balance followed by a retention of chloride. A negative balance similar to that observed with sodium, occurred after treatment was discontinued, but the diruesis was more sustained and balance was not established until nine days following cessation of cortisone.

Serum chloride values showed no significant changes throughout the study.

c. Potassium Balance.

Following the establishment of potassium balance during the control, cortisone was observed initially to induce a negative urinary

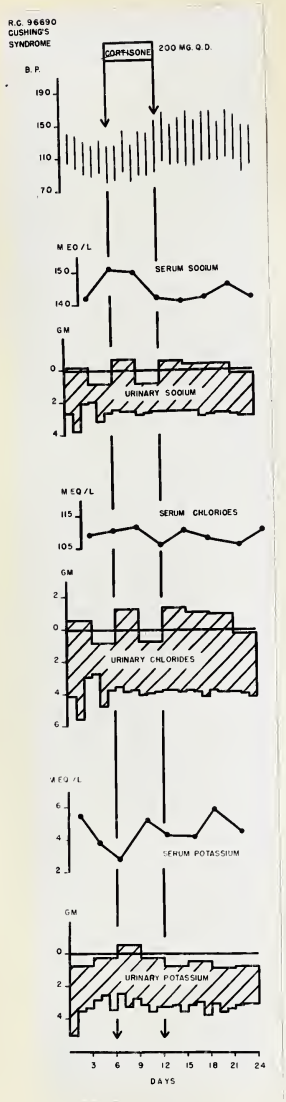


Figure 7.

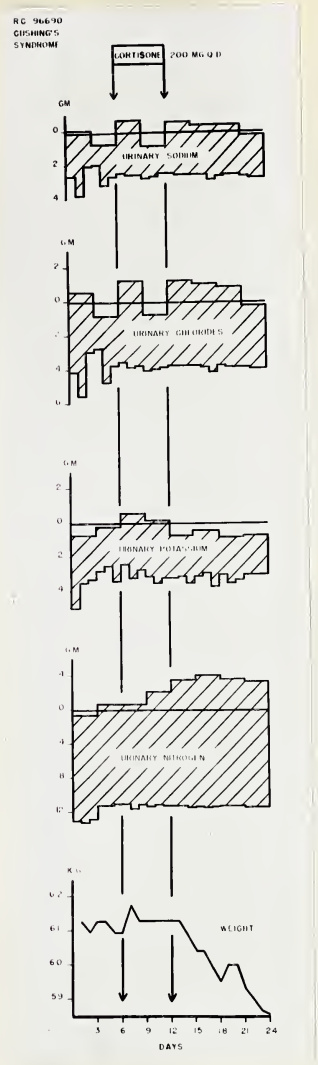


Figure 8.

Metabolic data on Mrs. R. C. #96690 with Cushing's Syndrome, to show the effect of therapy with Cortisone.

Metabolic data in this and later figures are arranged according to the scheme of Albright (125). There is a horizontal base line, intake is charted on a reverse scale downwards from the base line, the urinary excretion is then measured from the intake line upward towards the base line. If the output exceeds the intake the final level will be below the base line. Thus, a positive balance will be indicated by a clear area above the base line; a negative balance by a shaded area above the base line.

potassium balance accompanied by a lowered serum potassium level. During the last period on cortisone the serum potassium again returned to pre-treatment levels, at which time there was an urinary retention of the ion, which persisted throughout the post-cortisone control period.

(2) The Effect of Cortisone on Weight and Nitrogen Metabolism (Fig. 8).

The administration of cortisone resulted in a negative nitrogen balance of increasing magnitude. Following therapy there was a continued loss of 4 grams of nitrogen per day accompanied by a corresponding loss of weight.

(3) The Effect of Cortisone on Cortin, 17-Ketosteroids and Eosinophils. (Fig. 9).

Urinary cortin and 17-ketosteroid outputs were increased during cortisone administration. The cortin level rose from pre-treatment levels of 2 mgm. per 24 hours to 5.5 mgm. per 24 hours, and twelve days after therapy was still 2.5 mgm. per 24 hours. The 17-ketosteroid output rose from a control level of 15 mgm. per 24 hours to approximately 25 mgm. per 24 hours, and following therapy gradually returned to pre-treatment levels.

The eosinophil count showed a prompt fall when cortisone was begun and remained depressed following therapy.

(4) Other Effects of Cortisone in Cushing's Syndrome.

(See Appendix III Table I)

A sustained blood pressure elevation (Fig. 7) was noted following cortisone administration. From pre-treatment levels of 130/80, the blood pressure rose to levels of 170/100 and continued to be elevated after termination of the experiment.

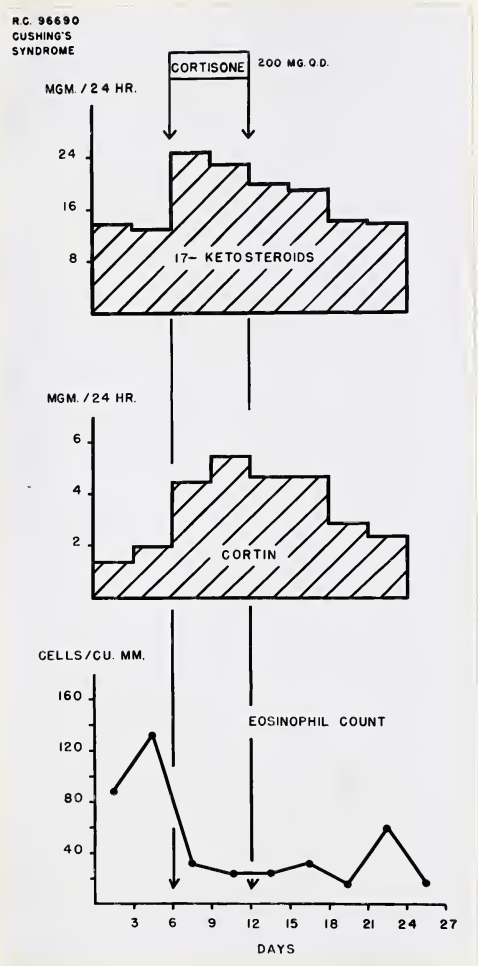


Figure 9.

Metabolic data on Mrs. R. C. #96690 with Cushing's Syndrome showing the effects of Cortisone on Urinary 17-Ketosteroid excretion and circulating eosinophils.

There were no significant changes observed in urine volume and specific gravity measurements. Fasting blood sugar levels remained within the normal range, but rose from a mean pre-treatment level of 79 mgm.% to an average of 96 mgm.% during therapy. A marked leucocytosis, in the absence of any demonstrable infection, was observed during cortisone therapy, the white blood count rising from a mean pre-treatment level of 5900 to 10,180 cells per cu. mm. Very slight elevations in urinary creatinine excretion were noted accompanied by a slight increase in total serum proteins.

(e) Discussion.

Plasma electrolyte disturbances occuring in Cushing's syndrome have been described (343)(344). Among those which have been noted are low serum potassium and serum chloride levels accompanied by elevated serum sodium levels, and on elevated CO_2 combining power. Urinary loss of potassium may be so great as to induce a hypopotassemic alkalosis (344). On the other hand Power and Kepler (344) have reported that the electrolyte picture found in Cushing's syndrome is most often essentially normal. The present case showed no marked abnormality of the serum electrolyte pattern, and the urinary excretion of electrolytes was within normal limits throughout the control, although the patient had not been taking methyl testosterone for three months previously. Further the mean cortin value for the control period was only slightly above the established normal range for the methods of assay used in this center. These facts suggest that the patient was in remission at the time of this study.

In most respects the patient responded in a normal manner to the administration of cortisone. However, sodium diruesis, rather than retention, was observed during the first period of therapy. This is not surprising for presumably the secretion of the other adrenal hormones was not impaired in this patient. It has been stated (345) that in the presence of other adrenal hormones sodium diuresis can occur, and that cortisone only shows a consistant sodium retaining effect in Addison's disease in the absence of DOCA therapy. Presumably the ability of this patient to produce her own DOCA accounts for the "paradoxical effects" noted.

The diuresis of potassium observed during cortisone therapy was not unlike that reported in a similar case treated with ACTH (342), or in normal patients treated with cortisone (127)(147). Accompanying the loss of potassium, which occurred only during therapy, was an increase in the urinary output of nitrogen which persisted some time after cessation of therapy, and resulted in considerable weight loss. Such a phenomenon has been observed in a patient with Cushing's syndrome treated with ACTH (346), but the reason for the apparent lack of parallelism between the potassium excretion and the nitrogen loss is not at present known. Interestingly enough during the period of most marked negative potassium balance the serum potassium level dropped to 2.8 meq./l. and no apparent clinical effect was observed.

The increase in the urinary output 11-oxysteroids (cortin) following cortisone administration to normal patients has been described by many workers (52)(127)(147). The elevated excretion of urinary corticoids observed was normal in this respect and is probably

due to the addition of exogenous "S" hormone to the endogenous production of that hormone by the patient. Cortisone administration usually results in a prompt fall in 17-ketosteroids (52)(147), however, elevated values were observed in this case and were probably due to measurement of some of the metabolites of cortisone in the determination of the 17-ketosteroids.

The pronounced drop in eosinophils was characteristic (147), and indicated that adequate dosage of the hormone was being administered.

(f) Summary and Conclusions.

A case of Cushing's syndrome (in remission) which responded in a normal manner to cortisone administration is described. There was an increase in the urinary output of 11-oxysteroids (cortin), with increased excretion of urinary potassium and nitrogen. Urinary sodium and chloride excretion was elevated initially, following which there was a retention of these elements. This "paradoxical effect" and an elevation of 17-ketosteroids, not usually observed, are discussed.

II. The Adrenogenital Syndrome Treated with Cortisone and ACTH.

(a) Introduction.

The adrenogenital syndrome, like Cushing's syndrome, is a form of hypercorticism usually associated with adrenal hyperplasia (347), or with adrenal neoplasm. It may occur at any time of life and in either sex, but is throught to occur more commonly in females (348). The characteristic feature of the condition is a tendency towards masculinity (349). However, the clinical picture of the syndrome depends

upon the sex and the age of the individual at the time of onset of the disorder (350).

Congenital hyperplasia of the androgenic zone of the adrenals, commencing in utero, results in macrogenitisomia praecox in males, and pseudohermaphroditism in females. In the case of the former, puberty is premature (351), but essentially normal in other respects. In females, however, defects in the orderly development of the urogenital tract occur. The clitoris is considerably enlarged and resembles a male phallus with hypospadias. Infantile female generative organs are present and, although no external vaginal opening is visible, a rudimentary vagina opens into the urethra. The way in which these abnormalities are induced by the over development of the Wolffian duct system and the suppression of the development of the Mullerian ducts, has been described by Young (352), who also points out that these unusual findings are associated with masculine habitus, hair and psychic outlook.

Maleness is superimposed upon genetic females, and accentuated in genetic males when the condition develops in childhood prior to puberty. Precocious puberty occurs, and in the male accelerated isosexual development produces increased genital growth (homologous pubertas praecox). In the female precocious heterosexual development results in a clinical picture (heterologous pubertas praecox) which includes hirsuitism, enlargement of the clitoris, a male escutcheon, acne, a male body configuration with prominent musculature, and a change in the character of the voice due to enlargement of the larynx and a thickening of the vocal chords (348). As the condition progresses in both sexes, there is rapid growth of the long bones, following which premature closure of the epiphyses

Figure 10.

Adrenogenital Syndrome #96696. Photograph showing facial hirsutism.

occurs, resulting in persons of short stature principally due to a shortness of the limbs.

In the adult male the adrenogenital syndrome is difficult to recognize and is often missed, but when it occurs in post-pubertal females masculinity is again apparent. A previously normal female develops hirsuitism, amenorrhea, an enlarged clitoris, flat atrophic breats, increased musculature and other evidences of maleness such as a male escutcheon, habitus and a coarse voice (349). Not infrequently there is diminished libido and a change of sexual interests from a heterologous to a homologous one (348).

It is thought that this type of hyperadrenocorticism, in contrast to the Cushing's type (123), is due to an excessive secretion of adrenal androgens ("N" hormones), which is reflected by a markedly elevated urinary excretion of 17-ketosteroids (123)(348). In most cases there are no carbohydrate or electrolyte disturbances (353), although some cases have been demonstrated to have electrolyte disorders causing symptoms similar to those of Addison's Disease (354), which have resulted in death (351).

The urinary output of 17-ketosteroids is presumably (123) an index of the production of the adrenal androgens which are responsible for the virilism seen in patients with the adrenogenital syndrome. As cortisone has been reported to reduce the urinary output of 17-ketosteroids (52)(147)(355), it was of interest to study the effect of this drug in a patient with this syndrome.

Figure 11.

Figure 12.

Adrenogenital Syndrome #96696. Photographs showing male musculature and body build of the patient. Note the small breasts and short extremities.

(b) The Effects of Cortisone on a Patient with the Adrenogenital Syndrome.

(1) Case History #96696.

The patient, Miss C. W., a female of 18 years of age, apparently developed normally until the age of nine years at which time it was observed that she was taller than other children her age and that there was increased growth of hair on her arms, legs and face. Acne and increased strength were also noticed at this time. Growth ceased at the age of eleven, and breast development and menstruation have never taken place. During the past year bilateral temporal recession of the hair line was observed. Aside from the above noted deviations she has enjoyed normal health, and to date is well adjusted to her condition.

On physical examination she was 131.0 cms. in height and weighed 47 kgs. Moderate acne and facial hirsuitism (Fig. 10) requiring that she shave every two days was apparent. Although there was a well developed widow's peak (Fig. 16), normal amounts of head hair were present. Her larynx was enlarged and her voice was low in pitch. Hypertrichosis, particularly of the abdomen, extremities, shoulders and about the nipples, and a male escutcheon were observed. Her body build and musculature were that of an athletic male (Figs. 11 & 12). The breasts were small and undeveloped, and her extremities were short due to early epiphyseal fusion. Pelvic examination revealed an enlarged clitoris and a small vagina and uterus. The ovaries were not palpable and no masses were noted elsewhere in the pelvis. Her blood pressure was within normal limits. No other unusual findings were noted.

Routine urinalysis and her hemogram were within the normal range. A lateral x-ray of the skull showed a normal sella and a chest

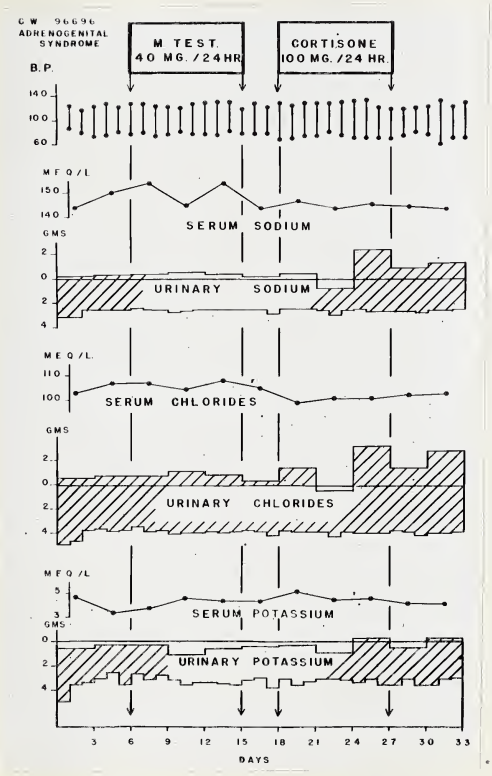


Figure 13.

Metabolic data on Miss C. W. #96690 with Adrenogenital Syndrome to show the effects of methyl testosterone and cortisone.

x-ray was normal. An intravenous pyelogram showed depression of the left kidney to a position lower than normal. A 17-ketosteroid determination performed on admission was 97 mgm. per twenty-four hours.

(2) Procedure.

Following a six day control period methyl testosterone (40 mgm. per day) was administered for nine days, after which the patient received no therapy for three days. At the conclusion of this period, ocrtisone (100 mgm. per day) was administered for three, three day periods. The patient was observed for a further interval of six days before her discharge. Subsequent to leaving hospital, weekly determinations of 17-ketosteroids were performed for two months. Six months later in an attempt to induce menstruation and breast development a course of oral cortisone (25 mgm. b.i.d.) was begun. Her progress was followed by 17-ketosteroid determinations, which were performed over an interval of two months duration.

(3) Results.

a. The Effects of Methyl Testosterone and Cortisone on Electrolyte Metabolism (Fig. 13).

(i) Sodium Balance.

Methyl testosterone had no appreciable effect on the urinary sodium balance. However, during the first two periods on cortisone there was a slightly negative balance for the first three days following which a slightly positive balance was observed. This was then folbwed by a pronounced diuresis of sodium, which persisted to a lesser degree for six days after cessation of therapy. The serum sodium values showed no significant alterations throughout the entire period of investigation.

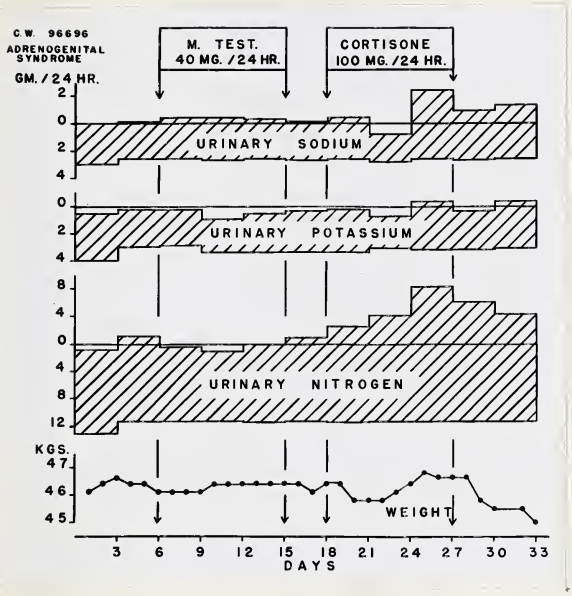


Figure 14.

Metabolic data on Miss C. W. #96696 with Adrenogenital Syndrome showing the effects of Methyl Testosterone and Cortisone.

(ii) Chloride Balance.

The urinary chloride balance closely followed the sodium balance in both magnitude and direction, except that there was a slightly negative balance of the element during the administration of methyl testosterone. Cortisone at first increased the urinary excretion of chlorides, after which there was a slight retention of chlorides for three days. During the first period on cortisone a marked diuresis of chlorides occurred, which continued until therapy was discontinued. The serum chloride values were observed to be slightly lower during the administration of cortisone, although the values remained within the normal limits.

(iii) Potassium Balance.

There was a slight retention of potassium during treatment with methyl testosterone and also during the first two periods of cortisone administration. This was followed by a slight diuresis of the element during the third period of cortisone therapy. Serum potassium levels showed no significant deviation from the normal throughout the study.

b. The Effects of Methyl Testosterone and Cortisone on Urinary Nitrogen and Weight (Fig. 14).

During testosterone therapy a slightly positive urinary nitrogen balance was observed, but there was no corresponding weight gain. Cortisone administration, however, produced a marked diuresis of nitrogen accompanied by a pronounced loss of weight. Following cessation of therapy, there was a gradual diminution in the urinary output of nitrogen, although the patient remained in negative nitrogen balance until conclusion of the study.

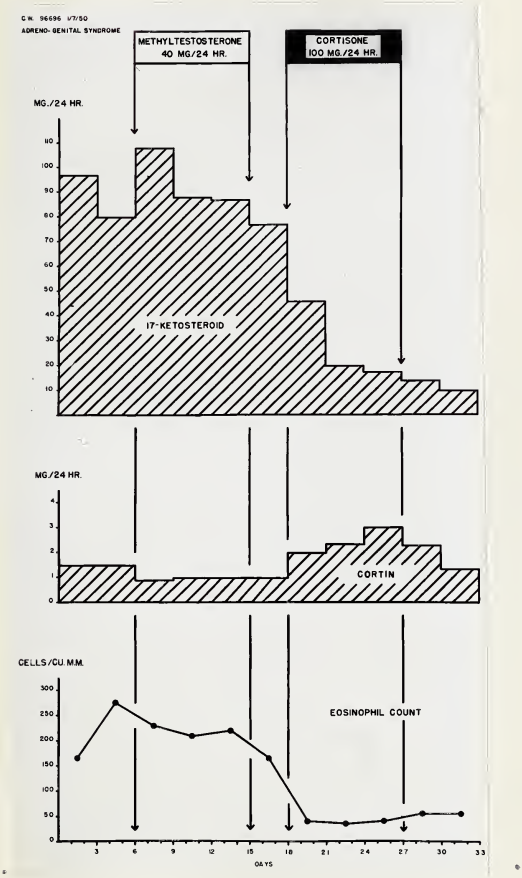


Figure 15.
Adrenogenital Syndrome C. W. #96696.

The effect of Methyl Testosterone and Cortisone on the urinary output of 17-ketosteroids and cortin, and on circulating eosinophil levels.

c. The Effects of Methyl Testosterone and Cortisone on the Urinary Excretion of 11-Oxysteroids (Cortin), 17-Ketosteroids and Circulating Eosinophil Levels (Fig. 15).

Cortin values were slightly lower during treatment with methyl testosterone, although they remained within the normal range. On cortisone therapy, however, there was a rise in the cortin level from a pre-treatment mean of 1.02 mgm. per twenty-four hours to 2.44 mgm. per twenty-four hours. The urinary cortin output returned to pre-treatment levels following cessation of therapy.

Methyl testosterone had relatively little effect on the urinary output of 17-ketosteroids. On the other hand cortisone therapy produced a dramatic decline in 17-ketosteroid output, from a mean pre-treatment level of 77.1 mgm. per twenty-four hours to a normal level of 11.9 mgm. per twenty-four hours at the termination of the experiment. Weekly determinations carried out following the conclusion of the study revealed that the 17-ketosteroids did not return to their pre-treatment level for sixty days.

The eosinophil count showed no changes during testosterone therapy, but a prompt fall was observed following cortisone administration. The level of circulating eosinophils remained depressed until termination of the study.

Menstruation and breast development, unlike that reported by Wilkins et al (353), did not occur following a second course of oral cortisone therapy of two months duration. Minimal dosage, however, again resulted in a pronounced decrease in urinary output of 17-ketosteroids from 69.5 mgm. per twnety-four hours to 17.3 mgm. per twenty-

Figure 16.

Figure 17.
Adrenogenital Syndrome Miss C. W. #96696.
Photographs showing appearance of acne before and after Cortisone therapy.

four hours, which rose to a level of 106.4 mgm. per twenty-four hours two weeks after cessation of therapy.

d. Other Effects of Methyl Testosterone and Cortisone (Appendix III, Table 2).

Therapy with methyl testosterone and cortisone produced no appreciable alterations in the carbon dioxide combining power of the plasma, total serum proteins, or blood pressure (Fig. 13). However, there was a slight rise in the fasting blood sugar level, which rose from a pre-treatment mean of 82 mgm.% to 91 mgm.% during cortisone therapy. Similarly cortisone administration produced a leukocytosis and slightly elevated hematocrit values, which were accompanied by a drop in blood hemoglobin from a pre-treatment mean level of 15.4 gms. to 14.7 gms. Urine specific gravity and creatinine determinations were slightly elevated during cortisone therapy, while the urine volume was slightly decreased.

A marked improvement of the patient's acne was noted during cortisone therapy (Figs. 16 & 17). However, with the gradual rise in the 17-ketosteroids after cessation of therapy the acne returned, although three months after discharge the severity of the condition was not as marked as before.

(4) Discussion.

Cortisone administered to the untreated Addisonian patient consistantly produces salt retention (345), but when used in the presence of other cortical hormones sodium diuresis may occur. The negative sodium and chloride balances (Fig. 13) observed during cortisone therapy may be explained on this basis, since the patient exhibited no

Addisonian symtoms or evidence of extreme sodium loss during the control interval. Presumably her endogenous production of DOCA-like hormones was sufficient to cause diuresis of sodium and chlorides when cortisone was administered.

The diuresis of potassium and nitrogen (Fig. 14) observed during cortisone therapy in this case has been observed by other workers.during therapy with methyl testosterone. However, potassium retention was greater than the retention of nitrogen observed. The opposite was the case during cortisone administration, as the nitrogen excretion was considerably greater than the small loss of potassium observed at the same time. The reason for this lack of parallelism is not completely understood, but in the case of the latter phenomenon is probably a reflection of the anti-anabolic effect of the "S" hormones on ingested rather than endogenous protein. Catabolism of endogenous protein results in release of the intracellular potassium and its loss in the urine is accompanied by a diuresis of nitrogen. On the other hand no potassium is released as a result of conversion of amino acids into carbohydrate, but the de-amination of these substances also results in an increased urinary nitrogen excretion. The observed findings are congruous with this hypothesis.

The apparently anomalous production of a weight gain coincident with a severe diuresis of nitrogen (Fig. 14) may be explained when it is noted that there was slight retention of water during the cortisone period (Appendix III, Table 2). On cessation of therapy the retained water was lost rapidly resulting in the weight loss which occurred during the progressive diminution of nitrogen loss.

The most striking feature in this case was the prompt and prolonged decrease in 17-ketosteroid excretion (Fig. 15) which was accompanied by a marked improvement in the patient's acne (Figs. 16 & 17). Apparently methyl testosterone does not produce the same adrenal response in the adrenogenital syndrome as it does in Cushing's syndrome (123). In the latter it usually depresses the 17-ketosteroids and also the excretion of corticoids. In the former it failed to depress the excretion of 17-ketosteroids and has only a slight depressant effect on the corticoid excretion.

The eosinophil response observed in this case was characteristic and was similar to observations made by other workers (152). Increased fasting blood sugar (147)(173) and serum protein (52)(147) have been observed to occur following cortisone therapy.

From this data it is concluded that these results are probably due to an indirect effect on an abnormal gland mediated through control of the anterior pituitary and regulation of ACTH production.

(5) Summary.

The effects of methyl testosterone and cortisone in a case of adrenogenital syndrome occuring in a pre-pubertal female are described.

Methyl testosterone resulted in a slight decrease in the urinary output of corticoids, a slightly negative chloride balance and a greater retention of potassium than of nitrogen.

Cortisone produced increased urinary corticoid excretion and a prompt and prolonged decrease in 17-ketosteroid output, which was accompanied by clinical improvement in the patient's acne. A fall in circulating eosinophils and a greater diuresis of nitrogen than potassium occurred

Figure 18.

Adrenogenital Syndrome R. C. #99205. Photograph showing male body build and musculature.

following cortisone therapy. An attempt is made to explain the latter effect, and the diuresis of sodium and chlorides observed is discussed.

It is concluded that the adrenal gland is abnormal in the adrenogenital syndrome, and that the observed responses are due to an indirect action of cortisone on such glands mediated by the anterior pituitary.

(c) The Effects of ACTH in the Adrenogenital Syndrome.

(1) Introduction.

It was concluded from the data obtained in the previous investigation that the depression of 17-ketosteroid excretion was due to an indirect effect of cortisone on an abnormal gland. To test this hypothesis and to gain more information concerning the mechanism responsible for the depression of the 17-ketosteroid output, it was of interest to determine the effects of ACTH in a patient with the adrenogenital syndrome.

(2) Case History #99205.

The patient, Mr. R. C., age 8, was a pseudohermaphrodite born with congenital hypospadias for which considerable plastic surgery had been done to carry the urethra forward to the tip of the glans. Rapid growth, abnormal presence of abundant pubic hair and precocious mental development caused the parents concern, and at the age of seven a laparotomy was performed. It was thought at this time that a mass could be felt in the region of the adrenals. Although otherwise healthy, the patient was unaware of the reason for his hospitalization and investigation.

On physical examination the patient weighed 36 kgms. and was noted to have the body build and musculature of a male (Fig. 18). The

Figure 19. Adrenogenital Syndrome R. C. #99205. Photograph showing male phallus and female distribution of pubic hair.

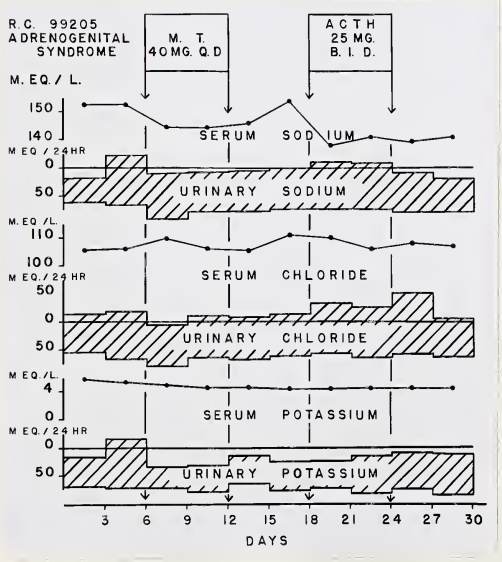


Figure 20. Metabolic data on R. C. #99205, with Adrenogenital Syndrome to show the effects of Methyl Testosterone and ACTH.

larynx was enlarged and his voice was deep, not unlike that of a fifteen year old boy. Axillary hair was present in fair quantity, and the pubic hair was female in distribution (Fig. 19). Pelvic examination revealed an enlarged phallus which bore evidence of considerable plastic surgery. The urethra opened on the under side near the glans. The scrotum was empty and the testes were not palpated. No masses were noted in the pelvis or abdomen. The blood pressure was within normal limits, and no other unusual findings were noted.

Routine urinalysis and the hemogram were normal. No intravenous pyelogram was done, and a chest x-ray revealed no abnormality. However, x-rays of the wrist, knee and ankle showed a bone age of about fifteen years. Psychometric studies revealed that the patient was of bright normal intelligence. On admission the 17-ketosteroids were 42.5 mgm. per twenty-four hours.

(3) Procedure.

Methyl testosterone (40 mgm. per day) was administered for six days, following an initial control period of the same length of time. After an interval of six days without any therapy, ACTH (25 mgm. b.i.d.) was given for two, three day periods, and on cessation of therapy the patient was observed for an additional six days.

(4) Results.

a. The Effects of ACTH and Methyl Testosterone on Electrolyte Metabolism.

(i) Sodium Balance (Fig. 20).

No change in the sodium balance was noted following the administration of methyl testosterone, and a very slight negative balance

was observed during ACTH administration. The serum sodium levels remained within normal limits throughout the investigation, except for the very low normal level which accompanied the slight diuresis of sodium during ACTH therapy.

(ii) Chloride Balance (Fig. 20).

There was a slightly negative chloride balance observed during the intial control period. Methyl testosterone produced a very slight retention of chlorides during the first period, and a slightly negative balance in the second period of therapy, which persisted throughout the second control interval. ACTH produced a more marked negative balance than had been observed during the preceeding control period, and following the cessation of therapy the diuresis of chlorides persisted for three days. No changes of significance were observed in the serum chloride levels.

(iii) Potassium Balance (Fig. 20).

Methyl testosterone administration caused a fairly marked retention of potassium in this patient, which persisted to a slight extent throughout the second control period. There was a slight retention of the element during ACTH administration, which was less marked during the six days folllowing the cessation of therapy. Serum potassium values remained remarkably constant throughout the study at a mean value of 4.76 meq./l. (S.D.$\pm$ 0.48)

b. The Effects of ACTH and Methyl Testosterone on Weight and Nitrogen Balance (Fig. 21).

There was no weight gain (Appendix III, Table 3) concomitant with the retention of nitrogen, which resulted during methyl

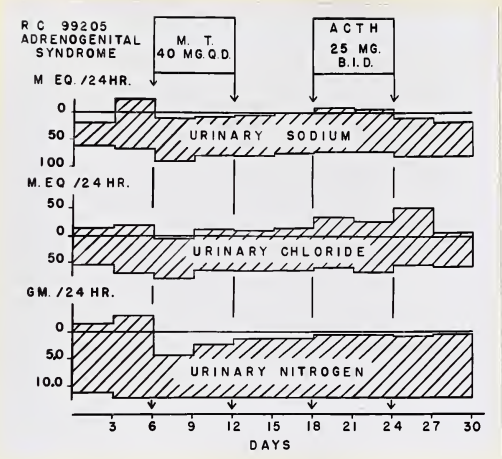


Figure 21. Metabolic data on R. C. #99205 Adrenogenital Syndrome to show effect of Methyl Testosterone and ACTH.

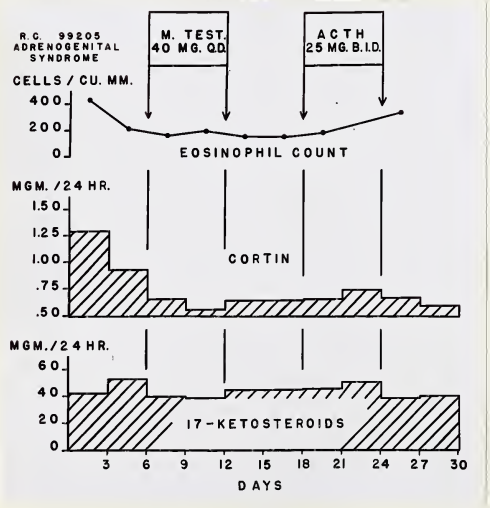


Figure 22. Adrenogenital Syndrome R. C. #99205. Chart showing effects of Methyl Testosterone on the urinary output of 17-ketosteroid and cortin, and on the circulating eosinophil level.

testosterone therapy. ACTH administration produced no change in the nitrogen balance, which had gradually returned to normal during the second control period.

c. The Effects of Methyl Testosterone and ACTH on the Urinary Excretion of Corticoids and 17-Ketosteroids and the Circulating Eosinophils (Fig. 22).

The urinary excretion of 17-ketosteroids was slightly depressed following the administration of testosterone, and showed only a small rise during the last three days of ACTH therapy. The cortin output, however, declined progressively during the control and was most markedly depressed during the last three days on testosterone. On cessation of therapy the depression of urinary corticoid excretion persisted and showed but a slight rise during the last period of ACTH administration.

There was no pronounced drop in the eosinophil level throughout the investigation.

d. Other Effects of Methyl Testosterone and ACTH (Appendix III, Table 3).

No marked changes were observed in urine volume, specific gravity or creatinine excretion, but there was a slight rise in blood pressure from a pre-treatment mean of 101/69 to 112/75 during ACTH administration. No clinical changes were observed.

(5) Discussion.

Throughout the study the patient co-operated well in collecting the specimens. However, it was noted that the volume of the last specimen of the fifth urine pool (115 c.c.) was much lower than those previously recorded (530 c.c.). A urine creatinine was performed and

confirmed the suspicion that the collection was incomplete. Unfortunately prior to completion of this test the three day pool had been mixed preparatory to starting various biochemical procedures. On questioning, the patient revealed that he had had difficulty voiding so had not completely emptied his bladder. Fortunately the next twenty-four hour collection was found to have a much greater volume (910 c.c.) than normal, and when calculated the mean of the two collections (512 c.c.) was approximately equal to the average daily output usually observed. On this basis it was decided to report the mean daily on cortin and 17-ketosteroid values for a six day interval, whereas electrolyte studies were reported as the mean daily values for a two and a four day pool respectively.

It was necessary to re-check several electrolyte determinations, as there was some suggestion that an error had been made. In each case where this was done (periods 1 and 3), frozen specimens were used (Appendix I), and the values obtained therefrom reported. As only one of the electrolyte figures was in doubt in each case, the remaining values served as checks on the accuracy of the repeated determinations. In both cases such checks were within the range of error for the methods used.

Apparently methyl testosterone has no appreciable effect on electrolyte balance (Fig. 20) except in the case of potassium, which was retained along with nitrogen during testosterone therapy. This data suggests that the retained potassium was utilized for protein anabolism, because the potassium did not remain extracellular as evidenced by the unchanged serum potassium level. That no concomitant weight gain occurred is unexplained.

The depression of 17-ketosteroids following testosterone was very slight when compared to the initial values observed during the control, and may possibly be attributable to the daily fluctuations observed in such determinations (232).

The apparent depression of corticoid excretion, which was observed following the use of methyl testosterone, is open to question. It is suggested that this depression was a continuation of the progressive decline which occurred during the control interval prior to the use of testosterone. Further studies are necessary to confirm this finding.

The effects of ACTH observed suggest that the dosage employed (152)(356) was inadequate in this case. Circulating eosinophil levels, which are used to indicate the adequacy of dosage, failed to drop during ACTH therapy (Fig. 22), and the urinary corticoid excretion, although slightly increased above the pre-ACTH control level, never exceeded the maximal excretion observed during the initial control period. Similarly the urinary output of 17-ketosteroids (Fig. 22) during therapy with ACTH never exceeded the highest level observed during the first control period. This data suggests that the adrenals were never sufficiently stimulated to produce the rise in corticoid excretion, and the drop in eosinophils usually observed following ACTH administration (147)(188)(206)(327).

Although minimal, some electrolyte changes were observed in this case. Sodium diuresis (Fig. 20), although not exceeding that observed during the first control period, did occur and was paralleled by a negative chloride balance. The cortin values obtained during ACTH therapy suggest that there was little "S" hormone activity, however, apparently sufficient was available to produce a slight diuresis of sodium and

chloride when acting with endogenous DOCA (345). Had there been no electrolyte regulating hormone produced by the cortex of the adrenals as in Addison's disease, there would have been sodium retention (345), although such retention has been reported to occur in normal individuals during ACTH therapy (147)(188).

The effects on potassium and nitrogen were unusual, but similar to those reported by Bartter et al (357). Retention of potassium was observed instead of the diuresis which usually occurs (147)(188)(189) and no nitrogen loss was noted. Although these abnormal responses probably were due to inadequate dosage, it is possible that the adrenal glands were abnormal and responded in an unusual way to minimal stimulation with ACTH. Indeed Bartter et al (357) have recently described abnormal responses to ACTH therapy in a case of adrenogenital syndrome. That no increase in the cortin output was observed suggested to these workers that ACTH in this syndrome had failed to stimulate the production of the "S" hormone. Eosinophil studies performed by them during ACTH therapy showed a slight but transitory drop following which the level returned to normal. Such a decrease would have been missed in the present study as the eosinophil counts were performed only on the second day of each three day period. Bartter's study (357), however, differed significantly from this one in that he observed a rise in the already elevated 17-ketosteroid levels. Failure to observe this is perhaps the strongest evidence in favor of the thesis that the ACTH dosage was inadequate. With this in mind it is hoped in the future to establish the minimal dosage level of ACTH which will produce definite evidence of

adrenal stimulation, at which time this study will be repeated to determine more definitely whether or not the adrenal cortex is normal in this syndrome. The possibility still exists that ACTH of a special type may result in a selective over production of the "N" hormone, which produces the symptoms characteristic of the adrenogenital syndrome.

(6) Summary.

A case of adrenogenital syndrome which responded in an abnormal manner to ACTH administration is described. There was very slight increase in the urinary output of sodium and chloride, a retention of potassium, and no loss of nitrogen or weight. Urinary excretion of cortin and 17-ketosteroids was very slightly elevated, but the circulating eosinophil levels remained unchanged. The probability that inadequate ACTH dosage produced the above results is discussed.

Methyl testosterone administration in this case resulted in a retention of urinary nitrogen and potassium, and a slight diuresis of chlorides during the latter part of therapy. Urinary excretion of 17-ketosteroids and cortin were slightly decreased. The possibility that the diminished cortin excretion was not a result of testosterone therapy is discussed.

(d) Comments on the Investigation of the Adrenogenital Syndrome.

The data at present available suggests two possible mechanisms by means of which cortisone acts to depress the urinary excretion of 17-ketosteroids in the adrenogenital syndrome.

1. Cortisone may by inhibiting ACTH production cause a decrease in the production of adrenal androgens.

2. Cortisone may act directly on the cells of the adrenal cortex, which are responsible for the excessive androgen production.

It has been suggested by Lewis et al (341) that the adrenal cortex is the primary site of the disordered function seen in the adrenogenital syndrome. Confirmatory evidence has been presented by Bartter et al (357), who have suggested that there is a diminished output of electrolyte regulating ("Na") and carbohydrate active ("S") hormones. It has been pointed out previously that the adrenal cortex responded abnormally with respect to electrolyte excretion (351)(354), and that ACTH administration failed to elevate the urinary excretion of corticoids in this and other studies (357). This evidence has been used by Bartter (357) to formulate a working theory explaining the pathogenesis of the adrenogenital syndrome and the mechanism of action of cortisone in these cases.

It is assumed that the "S" hormones are strong inhibitors of ACTH production, whereas the "N" hormones have but a weak inhibitory effect. Data presented (vide supra) using methyl testosterone as the "N" hormone seems to confirm this assumption, as the depression of 17-ketosteroids is greater with cortisone (an "S" hormone) than with methyl testosterone. Bartter (357) postulates that the primary defect is diminished "S" hormone production by the adrenal cortex, which results in a release of the normal inhbition of the anterior pituitary. Increased ACTH production occurs, which in turn results in the production of excessive amounts of adrenal androgens ("N" hormones). These produce the characteristic features of the condition, but fail to depress pituitary activity so the condition persists.

Wilkins et al (353) suggest that the action of cortisone is through the pituitary resulting in a suppression of ACTH, and thereby

causing a diminution in the secretion of the pathologic adrenals.

Evidence indicating a direct action of cortisone on the androgen producing cells is meager. However, atrophy of the zona reticularis by cortisone administration has been reported (358). This effect may be equally well attributed to an indirect action of cortisone via the pituitary. Wilkins et al (353) note that cortisone has been administered to normal and hypophysectomized rats treated with ACTH and state that in normal rats there was a reduction in the weight of the adrenals, while in the hypophysectomized animals maintained with ACTH showed no adrenal atrophy. This data further confirms the thesis that the action of cortisone is mediated through the anterior pituitary.

(e) Conclusions.

Sufficient evidence is not yet available to definitely state that cortisone reduces the elevated 17-ketosteroid output characteristic of the adrenogenital syndrome by suppressing of ACTH production by the pituitary. Although this mechanism is the most probable, more confirmatory work is required to establish it as fact.

III. The Effect of ACTH on Allergic Urticaria.

(a) Introduction.

Allergic urticaria is a condition of the skin characterized by the sudden appearance of an urticarial erruption accompanied by intense itching and/or burning (359). The erruption usually consists of discrete or coalescent wheals of various sizes, which vary in color from white to pale red. Often the condition is transitory, the lesions disappearing a few hours after onset only to recur some time later in either the same

or different areas of the body. Although allergins are sometimes demonstrated as the cause of the disorder, the precise mechanism by which it occurs is at present unknown.

However, recent studies of allergic phenomena have indicated the possibility of a hormonal relationship. Selye (360) has shown that purified ACTH will inhibit the "anaphylactoid" reaction, which is produced in rats by the parenteral injection of egg white. Control animals receiving no ACTH showed a marked edema of the nose, tongue and paws. Studies by Long and Favour (361) have indicated that ACTH will obliterate sensitivity reactions to tuberculin and the beta hemolytic streptococcus. More recently Nelson et al (362) have reported that the related substance, cortisone, inhibits anaphylaxis in the mouse. Similarly Dews and Code (363) have shown that cortisone decreased the severity and mortality of anaphylactic shock in adrenalectomized rats. Shwartzman et al (364) have reported that both ACTH and cortisone are able to suppress the phenomenon of local tissue reactivity in rabbits.

The increased availability of highly purified and potent adrenocorticotrophic hormone (ACTH) has established the fact that certain allergic syndromes respond favorably to its administration. Studies by Randolf and Rollins (365), Rose (366), Bordley et al (367) and other (368) have shown that bronchial asthma improves within a short time after treatment with ACTH is instituted. Carey et al (369) confirmed this observation when they demonstrated that stimulation of the adrenal gland by ACTH had a beneficial effect on the clinical manifestations of bronchial asthma. Samter (370) and Franklin (371) have indicated that

the improvement is proportional to the metabolic and hematological changes produced by the adrenal cortex, and is followed closely by an increase in the urinary output of 17-ketosteroids and 11-oxysteroids, and a decrease in circulating eosinophils. Further it has been reported by Carety et al (372) that the urticaria seen commonly in many hypersensitivity reactions to chemicals disappeared rapidly and completely under ACTH therapy. He points out that the mechanism responsible for these beneficial effects are as yet unknown, and notes that although the urticaria is blocked out, the cutaneous wheal and flare response following the injection of histamine is not altered with ACTH therapy.

Because few metabolic studies have been undertaken in this field and in order to obtain more information regarding the mechanism of the action of ACTH on allergic phenomena, it was of interest to study the effects of ACTH in a case of allergic urticaria.

(b) Case History #99254.

The patient, Mr. J. W., a female age 40, had no previous allergic manifestations until four years prior to admission, at which time she experienced her first attack of allergic urticaria. The onset was sudden and was preceded by the ingestion of a seafood cocktail. At first hives broke out on her arms, legs and face about four times a week and were relieved by benadryl. The attacks became more frequent and severe and soon were relieved only by daily use of neo-antergan. Since using neo-antergan she has been completely relieved, but when she stops her medication her urticaria promptly returns. The urticarial attacks begin with an intense pruritis, followed by raised erythematous wheals

Figure 23.

Figure 24.

Figures 23 and 24 - Allergic Urticaria Mrs. J. W. #99254. Photographs showing the effective control of urticaria with neo-antergan (Figure 23), and the appearance of the urticaria with no therapy (Figure 24).

which are sometimes clearly circumscribed and at other times confluent. The patient noticed that she was symptom free during her last pregnancy, which occurred two years prior to admission, and that she remained so until two days post-partum. She had a complete series of skin tests, all of which were negative.

Physical examination was essentially negative. She weighed 79.3 kgms. and appeared much younger than her stated age. The blood pressure was 120/80, and the heart was not enlarged to percussion. There were no thrills or murmurs and the pulse was 80 per minute. The integument was normal as she was receiving neo-antergan.

Her routine urinalysis and hemogram were within normal limits.

(c) Procedure.

Control observations were made for two, three day period while the patient was maintained on neo-antergan (100 mgm. per day), following which neo-antergan was discontinued for two days. Neo-antergan was then resumed for six days, five of which were unsuitable for biochemical determinations due to menstruation. After menstruation ACTH (25 mgm. q.8 h.) was administered for two, three day periods, and following one day of ACTH therapy neo-antergan was discontinued for the remainder of the investigation. The patient was observed for an additional six days after treatment with ACTH.

(d) Results.

1. Clinical Observations.

The patient was most comfortable while maintaining her daily intake of neo-antergan (Fig. 23). On cessation of this therapy she was bothered with urticaria. Erythematous itchy blotches appeared, accompanied

Figure 25. Allergic Urticaria, Mrs. J. W. #99254. Photograph showing the urticarial lesions on the back and shoulders.

by confluent wheals (Fig. 24)and were evident twenty-four hours after neo-antergan was stopped. These lesions varied in location and followed a wave like pattern with some areas showing marked urticaria while others were recovering from a previous attack. Nausea was noted during this period and was most severe when the pruritis was at its height. On resumption of neo-antergan relief was soon attained and within eight hours no lesions could be seen.

During the course of ACTH the patient was also bothered by pruritis, nausea and some edema. Once again the lesions were migratory and seemed to come and go in waves. Various parts were affected, but most commonly the extremities, back, shoulders (Fig. 25) and face showed the characteristic lesions. The first, third, seventh, ninth and eleventh days after beginning ACTH were the most bothersome. The remainder of the therapy period and ensuing control were spent in relative comfort. It can be seen that the effects of ACTH were not complete as the urticaria persisted, although it was less severe and frequent than in the period "off" neo-antergan.

2. The Effects of Neo-Antergan and ACTH on Electrolyte Metabolism (Fig. 26).

a. Sodium Balance.

During the control the patient was in sodium balance, but on cessation of neo-antergan there was a marked diuresis of sodium which was followed by a slight retention when therapy was resumed. During ACTH therapy there was a slight retention of sodium, after which a rebound diuresis of three days duration occurred following cessation of therapy. A positive balance was established during the last period of observation.

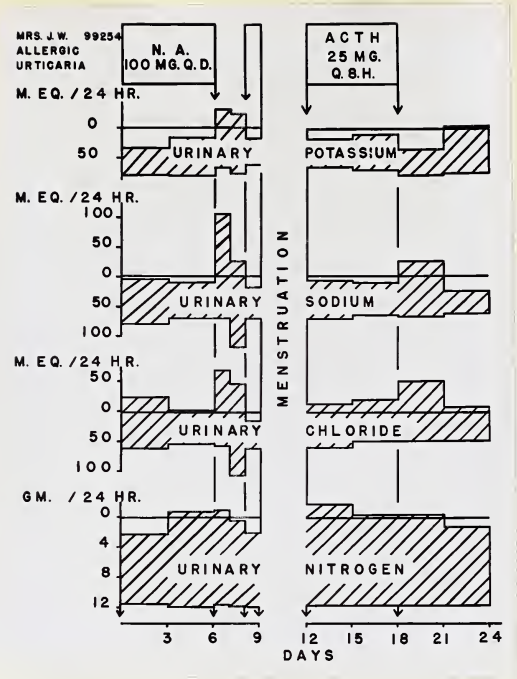


Figure 26. Metabolic data on Mrs. J. W. #99254 with Allergic Urticaria to show the effect of Neo-antergan and ACTH therapy.

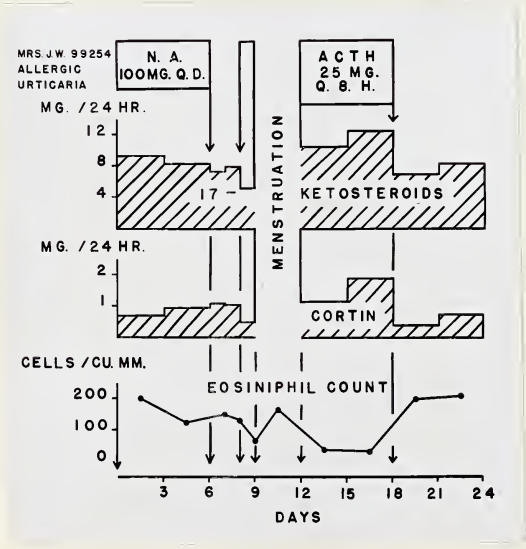


Figure 27. Allergic Urticaria, Mrs. J. W. #99254. Chart showing the effect of neo-antergan and ACTH on urinary output of cortin and 17-ketosteroids, and eosinophil levels.

b. Chloride Balance.

The output of urinary chlorides followed closely that of sodium. A slight diuresis of chlorides occurred during the first control period, following which a balance was established. A pronounced negative chloride balance occurred when neo-antergan was stopped, and a retention of the element was observed when antihistamine therapy was resumed. ACTH therapy produced a slightly negative balance, which increased further after ACTH was discontinued. A slightly negative balance was observed during the last control period.

c. Potassium Balance.

There was a positive potassium balance during the control which was followed by a prompt diuresis of the element after neo-antergan was discontinued. On resumption of therapy a retention of potassium was observed. Likewise ACTH produced slight potassium retention and after cessation of therapy a more markedly positive potassium balance was observed. Potassium balance was established during the last period of investigation.

Serum electrolyte studies were not performed in this case.

3. The Effect of Neo-Antergan on Weight and Nitrogen Balance (Fig.26).

There was no pronounced change in the nitrogen balance throughout the study. Equilibrium was reached after the first three days on neo-antergan, and there was a slight increase in urinary nitrogen during the first day following discontinuance of the drug. A slight retention of nitrogen was observed prior to resuming therapy at which time a more positive balance was established. There was a loss of urinary nitrogen for three days after ACTH was begun, following which a decreased urinary

nitrogen output occurred, which persisted until three days after the last ACTH injection. During the terminal period of observation a slightly positive nitrogen balance existed.

Throughout the study there was no change in the patient's weight.

4. The Effects of Neo-Antergan on the Urinary Excretion of Cortin and 17-Ketosteroids and Circulating Eosinophil Levels (Fig. 27).

Urinary excretion of cortin and 17-ketosteroids showed no appreciable change until ACTH was begun. During this period there was a significant rise in the output of both corticoids and 17-ketosteroids, which was slightly depressed following termination of ACTH therapy.

There was no marked change in the eosinophil level during or after neo-antergan. However, there was a marked drop in the circulating eosinophil level during treatment with ACTH.

5. Other Effects of Neo Antergan and ACTH (Appendix III, Table 4).

There was a slight decrease in urine volume accompanied by an increased specific gravity following ACTH administration, but no changes in blood pressure were noted during the study.

(e) Discussion.

It is interesting to note that this case (vide supra) failed to respond as dramatically as did the cases cited by Carey et al (372). The possibility exists that ACTH was not given frequently enough or at dosage levels sufficient to produce a marked and definite effect. However, on the basis of the cortin, 17-ketosteroid and eosinophil responses, it is assumed that adrenal cortical stimulation occurred. Tulpian (373) in studying the effect of ACTH on mycosis fungoides noted that although

the hormone failed to control the condition, it caused a decrease in pruritis. Although in this study ACTH failed to completely relieve the condition, it resulted in a reduction both in the intensity and frequency of the urticaria.

The effects of ACTH on sodium and chloride balances are variable (147)(367)(374), although retention of these elements usually occurs following ACTH administration. This has been confirmed by Bartter (374), who also reported a retention of potassium and noted that following ACTH therapy a diuresis of all three electrolytes occurred. The results obtained in this study are somewhat incongruous with the reported observations in that a retention of sodium and potassium occurred during ACTH administration, and following cessation of the hormone there was a diuresis of sodium and chloride but not potassium. Such findings are as yet unexplained.

The parallel relationship observed to exist between sodium and chloride balances has been described (147)(367).

The electrolyte responses observed following (a) the cessation of neo-antergan, and (b) the cessation of ACTH are remarkably similar in direction with the exception of the potassium response. A retention of this element occurred following ACTH therapy, whereas a marked diuresis was observed following discontinuence of neo-antergan. The cause of this loss of potassium perhaps may be explained on the basis of an elevated serum potassium, which could result from cell damage due to the hypersensitivity reaction occuring at this time. Unfortunately no serum studies were performed and this confirmatory evidence is lacking. However, the fact that ACTH resulted in a clinical improvement when neo-antergan therapy

was omitted, suggests that the potassium retention may be a biochemical reflection of the clinical response. Further the diuresis of sodium and chlorides, which occurred following cessation of neo-antergan (Fig. 26), was more marked than that which followed the course of ACTH. The degree of difference roughly paralleled the difference in the clinical response observed with the two drugs. It was seen that neo-antergan was the more effective agent.

A slight diuresis of nitrogen was accompanied by a loss of potassium following cessation of neo-antergan. However, this relationship was not observed following therapy with ACTH. The slightly negative nitrogen balance which occurred in the face of potassium retention cannot be satisfactorily explained, but it is thought that the retained potassium was probably not utilized by tissue anabolic processes which would have incurred a concomitant retention of nitrogen.

A drop in the level of circulating eosinophils has been shown by Randolf (327) to be a reliable indicator of the action of ACTH on the adrenal cortex. In the present study there was a drop in the eosinophil level along with an increase in cortin and 17-ketosteroid levels. Apparently the degree of adrenal cortical stimulation was not as marked as that produced during the patient's last pregnancy, for her relief was not as marked as that obtained at that time. It is suggested that higher ACTH dosage may have raised the cortin production sufficiently to produce a clinical remission similar to that previously observed during pregnancy. The pronounced depression of 17-ketosteroid and cortin levels immediately following ACTH was in contrast to the results reported by Forsham et al (375).

(f) Summary.

A case of allergic urticaria which responded moderately well to ACTH therapy is described. The clinical improvement observed was associated with increased urinary output of corticoids and 17-ketosteroids and a drop in circulating eosinophils. A slight retention of urinary potassium and sodium, and a diuresis of chlorides also were observed.

Comparison of potassium responses after cessation of ACTH and neo-antergan suggested the possibility that the clinical improvement was in some way associated with this element. Such a possibility is discussed.

The similarity of action of ACTH and neo-antergan is reported. It is suggested that higher ACTH dosage would produce greater clinical improvement than that observed.

This study, although not as dramatic in nature as others reported, served to emphasize the possibility that the basic mechanism of allergic disease may be closely related to the pituitary-adrenal system.

IV. The Effects of Cortisone on Iodiopathic Epilepsy.

(a) Introduction.

Epilepsy has been defined as a symptomatic paroxysmal cerebral dysrhythmia, which is characterized clinically by a loss of consciousness, involuntary muscle movement and an amnesia for the event (376). The symptoms of epilepsy are divided into three main groups: those characterizing the grand mal (major attack), the petit mal (minor attack), and the epileptic equivalent (psychomotor epilepsy).

The grand mal attack is characterized by the sudden onset of convulsions, which may be preceded by either a vague or a definite aura. In some individuals the onset is heralded by a headache or nervousness, whereas in others numbness or tingling in particular limbs or visual disturbances occur. The actual attack is sudden. The body becomes hypertonic and rigid and the jaws tightly clamped, the pupils become dilated and fixed, and the face congested. Following the tonic phase, which lasts twenty seconds, is the clonic phase during which the muscles relax and contract rapidly and there is usually loss of bowel and bladder control. Following the clonic phase the patient becomes exhausted and stuporous, after which consciousness returns and the patient complains of a severe headache, which may persist for hours or days.

A petit mal is usually of only a few seconds duration during which the individual loses consciousness, but doesn't fall. Following the attack the patient resumes activity where he left off as if nothing had happened and has no recollection of the episode.

Epileptic equivalents are characterized by the performance of purposeful acts, some of which may be violent and of which the individual is unaware.

A great many well recognized conditions such as brain tumors, trauma, cerebral vascular accidents, congenital brain defects, toxemia, cerebral edema and asphyxia may produce epileptic symptoms. However, a number of cases are without demonstrable etiology. Treatment of such cases of idiopathic epilepsy is extremely difficult, and is impeded by a lack of knowledge concerning the physiology which produces spontaneous generalized convulsions.

It is known that epilepsy is an outward manifestation of profound electrical disturbances of the cerebral cortex, and that there is a difference, even in the asymptomatic state, in the electroencephalogram observed in grand mal, petit mal and the various psychomotor variants. These disturbances are thought to be due to a defect in cell membrane function or structure (377), but the exact mechanisms which produce the disturbed electrophysiochemical activity underlying the condition are at present unknown. Many phenomena have been directly associated with the production of epilpetic seizures. However, only recently attention has been directed towards endocrine relationships to idiopathic epilepsy.

In 1931 McQuarrie and Peeler (378) introduced a test for idiopathic epilepsy based on a susceptibility to seizures following a low salt diet and acute hydration. It was later reported that increased cellular hydration lowered the seizure threshold (379) in electroshock and drug induced convulsions, and that changes in extracellular fluid volume when accompanied by changes in electrolyte concentration had no effect on such thresholds (379)(380). Later work suggested that the extracellular sodium (381) and chloride concentrations were more closely related to seizure thresholds than several other factors studies (382). Cerebral excitability was reported to be related to an increased serum sodium level similar to that produced by DOCA administration (383). The implication that the susceptibility to convulsions is related to such phenomena (384)(385) suggested the possible therapeutic value (383) of a hormone such as DOCA, which causes sodium retention (111)(133) and helps to maintain the extracellular fluid volume.

The anticonvulsive effects of DOCA have been demonstrated repeatedly in animals (381)(386)(387) since McQuarrie et al (377) reported that DOCA protected two patients with convulsive disorders against both the convulsive effects and alterations in electrolyte balance produced by pitressin. Aird (141) using sublingual DOCA in propylene glycol failed to confirm these results (377), but recently he reported considerable success following the use of DOCA tablets in epileptic patients (388). DOCA has been noted to increase the threshold to electroshock seizures in the rat (255)(399), an effect which was surprisingly antagonized by ACE or ACTH (255). In the cat DOCA afforded protection of limited duration against convulsions induced by cocaine, but not electricity (141), and in the rat prevented both the convulsions and pulmonary edema after metrazol treatment (400). Such actions resembled those of DOCA in preventing water intoxication symptoms (401) among which are violent convulsions.

The relation of DOCA to seizure thresholds is further indicated by the fact that the alterations of the electroencephalogram are similar in water intoxication and in epilepsy, and certain phases of the former can be relieved by DOCA (402). While the beneficial effects of DOCA in epilepsy (377) (388) have been attributed to sodium and chloride retention (377). More recent investigations have suggested the possibility that the reduction of brain potassium (403) induced by DOCA may be responsible for the anti-epileptic phenomena. Evidence supporting this thesis has been presented by Cicardo (404), who demonstrated elevated serum potassium levels in the longitudinal sinus of dogs during a seizure. Micro incineration techniques have shown that the loss of potassium during seizures is

compensated for by a gain in sodium (387). Further low potassium diets have been shown to protect rats against audiogenic convulsions.

Although no comprehensive statements concerning the role of the adrenal cortex in electrolyte and water metabolism in the various convulsive states can be made as yet, the possibilities are intriguing. This is particularly true in view of the accumulating evidence that the cortical hormones have important functions in regulating the electrical activity of the brain (126). Desoxycorticosterone glucoside (DCG), an active water soluble preparation of desoxycorticosterone, has been shown to reduce the electroencephalographic abnormalities of epileptics (388). Further Klein et al (405) have shown that DOCA and ACTH have similar effects on the electrolytes and encephalograms of patients subject to convulsive seizures. Considerable electrographic improvement was observed by these workers following the use of these agents.

In view of the paucity of clinical material reported and the increasing interest in the neurophysical and biochemical mechanisms influencing convulsive activity, this investigation was undertaken.

(b) Special Methods.

Several specialized techniques, not previously described, were used in this case. The electrolyte composition of feces, a full day's diet, and sweat samples obtained from the hand and forearm were determined. The sweat was collected using a modification of the technique used by Conn (144), and the diet and feces specimens were treated in the manner of Wallace et al (337). Flame photometry was used for the sodium and potassium determinations, and the chlorides were measured using the method of Schales and Schales (332), as modified by Schales and Schales (406). A cellular

potassium determination was performed on centrifuged erythrocytes, which had been hemolyzed in sodium free distilled water. Electroencephalograms were recorded at appropriate intervals during the investigation of this patient, and at least one hour post cibo to avoid the possibility of hypoglycemia.

(c) Case History #81123.

The patient, Mr. M. A., age 49, gave a history of convulsions at age 1½, following which he was well until the age of 24 when he was thrown from a horse and dragged some distance. Following this episode, which according to the patient resulted in a fractured skull, he recovered and remained well for a period of six years at which time he had his first epileptic seizure. Two more similar attacks occurred during the ensuing year, and gradually throughout the next seven years their frequency increased. At this time the seizures occurred at regular intervals of ten days when he would have four to five seizures on a single day following which he would be seizure free for another ten days, when the cycle would be resumed. This pattern continued until four years prior to the present admission, at which time he was hospitalized and treated with dilantin. Following his discharge at this time the attacks became progressively less frequent over a period of seven months. He was then free of seizures for eleven months after which his attacks again returned four to five times a day at two week intervals, and to date this cycle has persisted.

The onset of an attack was usually heralded by a frontal headache which occurred from twelve to twenty-four hours prior to the convulsion. His aura varied, but usually consisted of a sense of constriction

in either his chest or "stomach" followed by a pain at the back of his head, and a "burning sensation" at the back of his nose. Often he managed to grab his nose with his left hand before losing consciousness. His head, eyes and the corner of his mouth have been observed to twist to the right during a severe seizure. The convulsions were generalized and lasted for about five minutes, during which time, until recently, he lost all sphincter control. The post-ictal depression was characterized by weakness and a headache of two to three hours duration.

The patient gave a history of nocturia and a susceptibility to infection, having had pneumonia six times, peritonitis following an appendectomy and frequent occurrence of "sinus trouble". In addition he claimed to be allergic to cattle and dust and to have "asthma", which was more pronounced during wet weather. The family history was non-contributory.

On physical examination the patient was suspicious and moderately paranoid, but was co-operative. He weighed 57 kgms. There was slight injection of the pharnyx, tenderness of the right maxillary and frontal sinuses and moderate turbinate hypertrophy, although no post nasal drip was observed. The thyroid was slightly enlarged, but was freely moveable. The chest was normal, and on percussion the heart showed enlargement to the nipple line. The blood pressure on admission was 142/104, and the fundi showed some arteriosclerotic changes with venous dilatation and slight A.V. nicking. The heart sounds were of good quality and the pulse regular and full. The abdomen bore a midline scar, but was otherwise normal. The left ankle was inverted slightly and showed marked limitation of movement as a result of damage incurred

when dragged by a horse. No neurological impairment was noted, although all reflexes were hyperactive.

Routine urinalysis and the hemogram were within normal limits. X-rays revealed no abnormality of the skull. The electroencephalogram showed a fairly pronounced generalized cerebral dysrhythmia, which was most severe in the right posterior head region. A pneumoencephalogram series done two years previously was essentially normal. The patient continued on dilantin (1½ grains t.i.d.) and mesantoin (100 mgm. t.i.d.) throughout the entire investigation to obviate the possibility of status epilepticus occuring.

(d) Proceedure.

The investigation to be described (vide infra) was carried out in three stages during which the effects of pitressin, diminished water intake and cortisone were observed. Initially it was intended to repeat the work of McQuarrie (37) following which it was hoped to observe the effects of cortisone in epilepsy. To this end the patient was studied for a six day control interval. The observations made during this period suggested that the patient had diabetes insipidus. To rule out this possibility, studies with DOCA were postponed and the patient was observed further with no change in therapy. Because of persistant polyuria, it was decided to observe the effects of pitressin on the urine output. The results of this test suggested that the patient was not producing sufficient enddgenous anti-diuretic hormone.

During the second period of investigation the pitressin test was repeated with essentially the same results as before, Although oliguria was observed, there was no alteration in the patient's desire to

drink water. This suggested that this was not a true case of diabetes insipidus, but that habitual intake of excessive amounts of water resulted in the observed polyuria. To test this hypothesis it was decided to restrict fluid intake to about 1500 c.c. per day (including water of oxidation and pre-formed water of food). Observations were carried out with this regimen for ten days following which the patient was discharged.

Following a one month period of observation as an outpatient, he was re-admitted for study. The low water regimen was continued and after a control period of one week cortisone was administered for thirteen days. After cessation of therapy the patient was observed for a further six days.

(e) The Effects of Pitressin on Epilepsy.

(1) A Note of Explanation.

Usually in studies of the sort described, the urine investigations are performed upon three day pools. It is obvious then that in every week, one day could be permitted to pass during which no analyses were done. In the previous studies the dietary intake and therapy regimens were maintained constant throughout this day, so that the balances would be unaltered when measurements were again begun. It became apparent when the data described (vide infra) was studied that some additional intake of the measured elements was interfering with the establishment of a balance. Careful questioning revealed that the patient had been fed routine hospital diet on these days, thus accounting for the peculiarities of the curves obtained. However, the data resulting from this period of study is reported, as it is believe that the effects of pitressin were unaffected by this error. To confirm this belief, however, the pi-

tressin test was again repeated at a later date. Further, some of the electrolyte data is of interest when considered as an adjunct to similar data reported later in this paper.

(2) Results.

a. The Effects of Pitressin on Electrolyte Metabolism (Fig. 28).

i. Sodium Balance.

Throughout the control period there were no pronounced disturbances in the sodium balance, with the exception of those attributable to the excess dietary sodium obtained at the beginning of each week. Where daily balance determinations were done during an interval in which convulsions occurred, there were no significant changes in the sodium balance. During pitressin administration, however, there was a marked diuresis of sodium, which was greater than any sodium loss observed during the previous three weeks. After cessation of pitressin therapy there was a positive sodium balance for one day following which there was a slight diuresis of the element.

Serum sodium levels (Appendix III, Table 5) were elevated throughout the study except during the initial control week and the day following the pitressin test.

ii. Chloride Balance.

The chloride balance closely followed that of sodium. During the control all changes observed were attributable to the error previously mentioned (vide supra). Convulsions in the third week resulted in a diminished output of chlorides, and on the day following there was a slight positive balance of the element. Pitressin administration resulted in a pronounced diuresis of chlorides following which there was

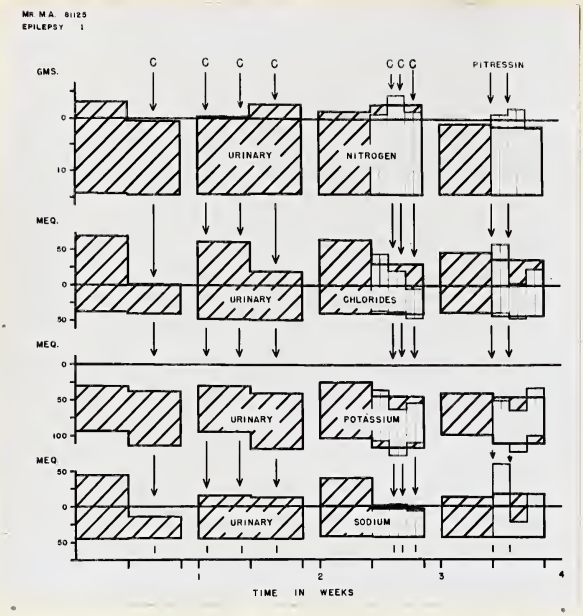


Figure 28. Metabolic data on Mr. M. A. #81123 with epilepsy to show the effect of pitressin.

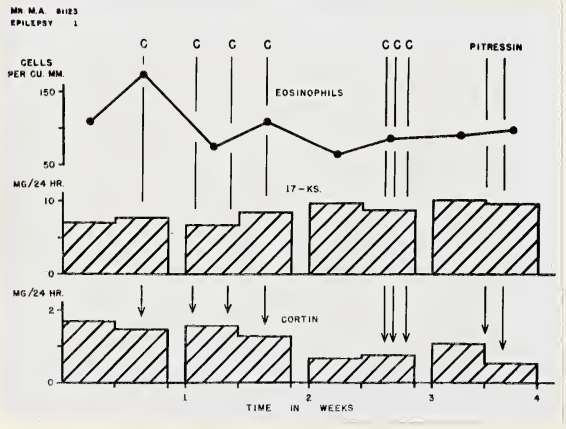


Figure 29. Idiopathic epilepsy #81123 showing the effect of pitressin on the urinary output of cortin and 17-ketosteroids, and on the circulating eosinophils.

a considerably diminished loss of the element. During the last day of the study there was a moderate diuresis of chloride.

Serum chlorides (Appendix III, Table 5) were within the normal range throughout the study.

iii. Potassium Balance.

There was a marked and persistant retention of potassium throughout the entire study. An even greater positive balance was observed during and following seizures. Pitressin produced no significant changes in the potassium balance, although the urinary excretion was slightly less than the mean for the three day period in which the pitressin test was performed. Following the pitressin test there was increased retention of potassium for a day after which a slightly less positive balance was observed.

b. The Effect of Pitressin on Nitrogen Balance (Fig. 28).

During the control there was a slightly negative balance of nitrogen at the beginning of the first week, following which a balance was established for seven days. There was a slightly negative balance again during the latter part of the second week on no therapy. Seizures on the fifth day of the third week produced a negative nitrogen balance, which was slightly greater than any previous nitrogen loss observed during the control.

Following the pitressin a diuresis of nitrogen of approximately the same magnitude as that observed during the seizures was noted. A retention of nitrogen occurred two days after the pitressin test.

c. The Effect of Pitressin on the Urinary Excretion of Cortin and 17-Ketosteroids, and Circulating Eosinophil Levels (Fig. 29).

Throughout the entire study there were no marked changes in the excretion of 17-ketosteroids, and all the values remained within the normal range. Likewise the eosinophils showed no marked change, either during seizures or the administration of pitressin. The cortin values remained fairly constant (1.4 mgm. per twenty-four hours), until the third week during which the excretion dropped to less than 1 mgm. per twenty-four hours. The lowest value (0.54 mgm. per twenty-four hours) was observed following pitressin therapy.

d. The Effects of Pitressin on the Electroencephalogram (Figs. 37-39).

Throughout this period of investigation little change was observed in the electroencephalogram. The diffuse slow-wave cerebral dysrhythmia (notably 4 per second and reaching 120 microvolts) (Fig. 37 Tr. 5 & 6) was not made more pronounced by pitressin administration, although the right sided parietooccipital localization of the disturbance was slightly less evident during pitressin therapy (Fig. 39 Tr. 17 & 18), than in the previous records (Fig. 37 Tr. 1 & 2). Abnormal electrical activity was observed on the left side (Fig. 38 Tr. 13 & 14) on one occasion due to release of the suppression normally present resulting from anticonvulsant mediciation, which was omitted by the patient prior to making the tracing.

e. Other Effects of Pitressin (Appendix III, Table 5).

The administration of pitressin produced an elevation in blood pressure from a pre-treatment mean of 125/89 to 131/93, and a marked retention of water which resulted in a weight gain of apporiximately 1.2kg.

(3) Discussion.

Although the electrolyte data was difficult to interpret due to imperfect technique (vide supra), it was interesting to note that results similar to those reported by McQuarrie et al (377) were observed following pitressin administration. The diuresis of sodium and chlorides (Fig. 28) is particularly noteworthy in view of the fact that the effect is opposite in direction to that observed when DOCA is used (407). It was this observation that led McQuarrie (377) to the clinical trials of DOCA in the therapy of epilepsy. The retention of potassium observed has also been reported (377) to follow pitressin therapy. That this occurred at a time when there was a loss of nitrogen suggests that these two actions were independent. A similar independence was observed during the occurrence of seizures, and is at present unexplained. Further the retention of potassium observed during seizures is incongruous with the findings of Cicardo (404), who noted an elevated serum potassium during a seizure.

The drop in cortin (Fig. 29), which occurred following the use of pitressin, suggests the possibility that this drug inhibited certain functions of the anterior pituitary. However, the results are inconclusive as the depression was not marked and, in view of the previous downward trend, may have occurred in spite of the use of pitressin.

Pitressin was employed to determine whether production of the posterior pituitary anti-diuretic substance was adequate in this individual. The retention of water accompanied by an increase in weight suggested that the production of this substance was inadequate. However, the possibility that an excessive water intake was perhaps responsible for the large urine output initially observed still existed. Further in

view of the faulty technique employed in this investigation, it was decided to repeat the pitressin test. If the results remained unchanged, it was hoped to prove or disprove the hypothesis that a habitually excessive intake of water was responsible for the increased output, which was suggestive of diabetes insipidus. To test this thesis, a markedly reduced water intake was established and water balance studies undertaken.

(f) The Effects of Diminished Water Intake and Pitressin on Epilepsy.

(1) Results.

a. The Effects of Reduced Water Intake and Pitressin on Eledtrolyte Metabolism (Fig. 30)

i. Sodium Balance.

During the control period there was a retention of sodium of the magnitude of about 11 meq. per day. Administration of pitressin resulted in a pronounced diuresis of sodium following which a positive balance was established. The low water intake initially resulted in an even greater retention of sodium than was observed during the control. Gradually, however, the urinary output of sodium increased and five days after inauguration of a diminished water intake, the patient was in balance with respect to sodium.

ii. Chloride Balance (Fig. 30).

During the control interval a diuresis of chlorides was noted. Pitressin caused a slight reduction in the urinary loss of chlorides, although a negative balance was still observed. Following the reduction in fluid intake, the chlorides closely followed the changes observed in the sodium balance. There was a pronounced retention of urinary

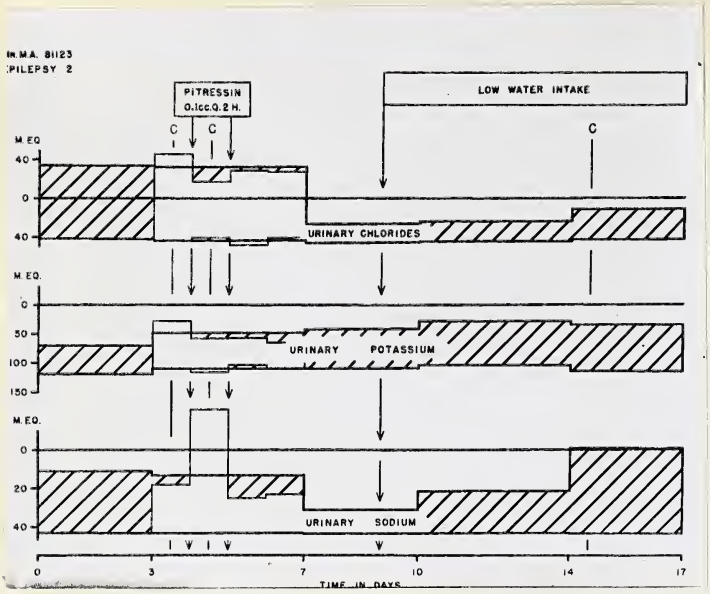


Figure 30. Metabolic data on Mr. M. A. #81123 with Epilepsy to show the effect of lowered water intake and Pitressin. N.B. C - convulsion.

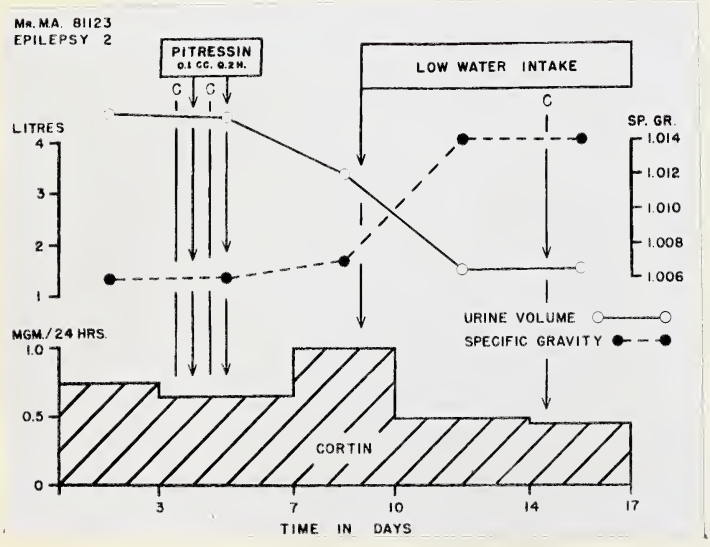


Figure 31. Chart showing the effect of Pitressin and lowered water intake on cortin excretion, and urine volume and specific gravity.

chlorides, which gradually diminished during the first five days after the low water intake was begun.

iii. Potassium Balance.

Again a retention of potassium was apparent throughout the entire study. During the three day control period an average of 70 meq. per day were retained. Pitressin altered this state very little producing no marked change in the potassium balance. The restriction of fluid intake was followed by an increased loss of urinary potassium, although the positive balance persisted.

(b) The Effects of Diminished Water Intake and Pitressin on Nitrogen Balance (Appendix III, Table 6).

There was no appreciable change in the nitrogen balance throughout this period of investigation.

(c) The Effects of Diminished Water Intake and Pitressin on the Urinary Output of Cortin and 17-Ketosteroids, and Circulating Eosinophil Levels.

Circulating eosinophil levels and urinary 17-ketosteroid output were unchanged by either the administration of the pitressin or the alteration in fluid intake, their mean levels throughout the study being 85 cells/ cu. mm. and 7.8 mgm. per twenty-four hours respectively. A very slight decrease in the excretion of Cortin was observed following the administration of pitressin. There was a slight increase in Cortin output prior to beginning the restricted fluid regimen, and during the seven days following water restriction the cortin values were slightly lower than those observed during the control interval.

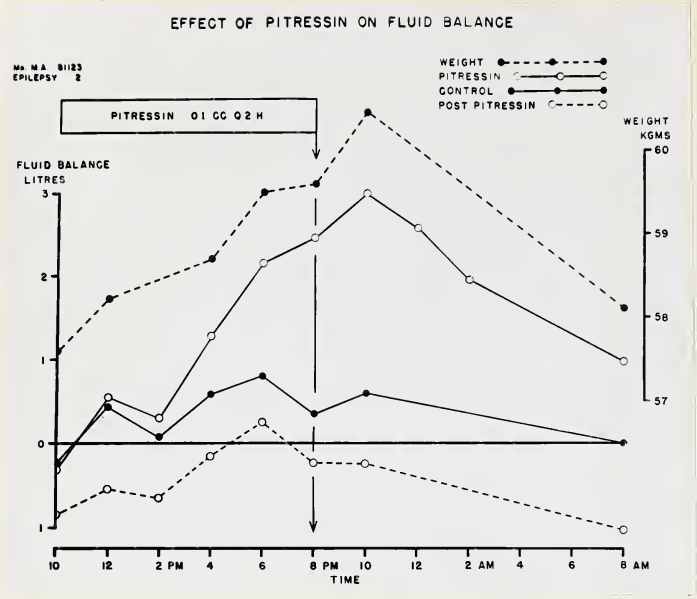


Figure 32. The effect of Pitressin on fluid balance.

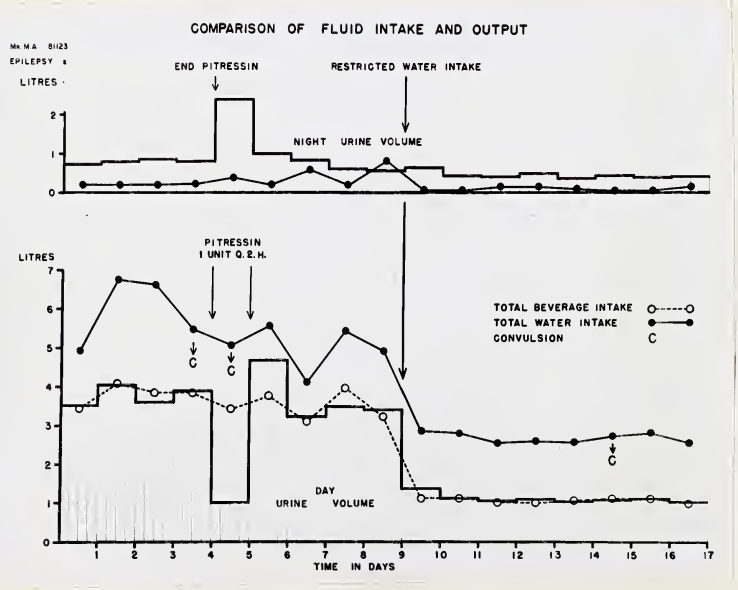


Figure 33. The effect of reduced water intake and Pitressin on fluid balance.

(d) The Effects of Pitressin on Fluid Balance.

During the four days prior to the administration of the cumulative water balance was calculated at two hour intervals and a mean curve constructed from these values (Fig. 32). Similar balances were calculated for the day of the test and the day following. A marked retention of water (2.5 litres), paralleled by weight gain of similar magnitude, was observed following the administration of pitressin (0.1 c.c. q. 2 h.) over a twelve hour period. A loss of water which approximated the retention induced by pitressin (Fig. 32) occurred. During the day following the test studies comparing the urine output with the intake of beverage water, and the total water intake (sum of beverage water, H_2O oxidation and pre-formed H_2O of food) also indicated retention of water during the administration of pitressin, which was followed by a prompt diuresis of similar magnitude during the twelve hours after cessation of treatment (Fig. 33). Comparisons of day and night urine volumes with water intakes throughout the study revealed that the day urine volumes (8:00 A. M. to 8:00 P. M.), for all practical purposes, were identical with the amount of beverage water ingested over the same interval. The amount of water ingested during the night, however, was considerably less than the amount of urine formed during that period. Presumably the water of oxidation and pre-formed water of food contributed to this loss. Such fluids lost in excess of the urinary output comprised the insensible water loss, which occurred through the lungs and skin. On a low water intake this relationship was unaltered, although the daily urine volume dropped from a mean output of 4500 c.c. to 1500 c.c. per day (Appendix III, Table 6), and the specific gravity of the urine rose from a pre-treatment mean of 1.006 to 1.014 (Fig. 31).

(e) The Effects of Lowered Water Intake and Pitressin on the Electroencephalogram.

During the control period of this investigation there was little substantial change in the electroencephalographic pattern from that observed during the previous period of observation. The slow-wave dysrhythmia remained diffuse (Fig. 39, Tr. 24), although voltages were slightly higher and more pronounced in the right occipital region (Fig. 39 Tr. 19). Pitressin aggravated the abnormality only slightly, and no seizure was observed in spite of the slightly increased electrical activity, which was apparent in the tracings (Fig. 40 Tr. 25 & 26).

Restricted fluid intake, however, resulted in a pronounced improvement in the electroencephalogram (Fig. 40 Tr. 27, 28, 31, 32). Delta wave voltage dropped from 80 microvolts to 40 microvolts and fewer delta (4 per second) waves (Fig. 40 Tr. 28) interrupted the normal alpha (10 per second) rhythm (Fig. 41 Tr. 34, 37, 38). The improvement in the electroencephalogram continued through this period of investigation.

(f) Other Effects of Reduced Water Intake and Pitressin.

Before pitressin therapy the patient was having seizures similar to those described in the history, approximately every two weeks. Usually the post-ictal depression was marked and the patient complained of pronounced weakness and was quite content to remain in bed following the seizures. During this pitressin test he complained of extreme weakness, which became progressively worse as the water retention increased. At the time of his final weighing (Fig. 32), immediately after the last injection of pitressin, he was unable to stand on the

scales without help. During the latter part of the afternoon he complained of a headache, which persisted throughout the remainder of the day. After the diuresis began he became progressively less weak and the following day was clinically the same as before the test.

Following the reduction in beverage intake, the patient complained less frequently of weakness. He reported that he was able to return to his work shortly after a seizure with little feeling of weakness. Following his discharge, the patient undertook to perform very heavy work such as clearing land and cutting cord wood. He reported at a later date that although his seizures were as frequent as before, they bothered him less and the feeling of weakness was much reduced.

(2)Discussion.

Unlike the first pitressin test (Fig. 28) no marked chloride diuresis was observed when the test was repeated (Fig. 30), and interestingly enough there was no marked change in the nitrogen balance during the therapy. Reasons for the differences between the two tests are not clear. However, the dosage may have been a factor. A dose of 2 units q. 2 h. was used in the previous test and may have accounted for the response observed at that time. The possibility that the "milieux interior" was not precisely the same during the two tests also must be considered. Variable responses to cortisone and ACTH have been explained in this manner by Ingle (#45), and such a possibility must not be omitted in these studies.

The diuresis of sodium, however, was a common factor observed during both pitressin tests (Figs. 28 & 30) and would suggest that DOCA and pitressin were antagonistic. Such a possibility has been entertained

by Gaunt et al (146), who also pointed out that the retention of water observed when DOCA is used is secondary to the retention of sodium produced by DOCA. They reported that DOCA acts to produce a water diuresis in animals on low salt diets.

Following the reduction in the fluid intake, the specific gravity of the urine was observed to rise (Fig. 21) indicating that the kidney was able to perform work. This suggested that the low specific gravities previously observed were due to excessive ingestion of fluids. The fact that pitressin produced a retention of fluid (Fig. 32) suggested that the patient had diabetes insipidus. However, failure of the patient to stop drinking usual amounts of water during pitressin therapy was evidence that the patient was accustomed to taking large amounts of fluid. This hypothesis was confirmed when a striking reduction in urine volume occurred following reduction of water intake (Fig. 33). The improvement in the electroencephalographic pattern (Fig. 40 Tr. 27 & 28) was encouraging, and the subjective improvement later reported by the patient paralleled similar observations by other workers (408)(409).

It was decided to keep the patient on a low fluid intake for a month, following which a new control level would be established and be sufficiently stable to permit studies with cortisone. The proposed DOCA experiment was dropped at this time due to the pressure of time.

(g) The Effects of Cortisone on Epilepsy.

(1) Procedure.

Following a control interval of one week, cortisone (200 mgm. q.d. I.M.) was administered for two days. The dose was reduced to 100

mgm. q.d. for an additional day, at which time the patient complained of extreme pain at the injection sites. In view of the possibility of infection (410), the drug was administered orally and the dose elevated to 150 mgm. q.d. to overcome the expected difference in potency (411)(412). This was carried on for four days at which time it was noted that there had been a rise in the eosinophil count. This was found to be due to inadequate dosage, so the dose was doubled, and oral cortisone (300 mgm. q.d.) administered for six days, following which the patient was observed for an additional six days before being discharge.

(2) Results.

a. The Effect of Cortisone on Electrolyte Metabolism (Fig. 34).

i. Sodium Balance.

During the first three days of the control there was a negative balance of 75 meq. per day, following which the patient was in balance for three days. Immediately before commencing cortisone there was a slightly positive balance of about 10 meq. per day. Intramuscular cortisone produced a marked retention of the element for three days, following which the patient began oral cortisone, and the urinary output of sodium increased. The patient remained in balance until the dosage was doubled, when a retention of sodium was noted, which persisted until cessation of therapy. During the first three day period with no therapy there was a prompt diuresis of sodium following which the patient remained in balance until discharge.

Throughout the study the serum sodium levels were subnormal with values of 124 meq./l. being recorded. During the control on cortisone, however, the serum sodium levels rose steadily reaching 132 meq./l. during

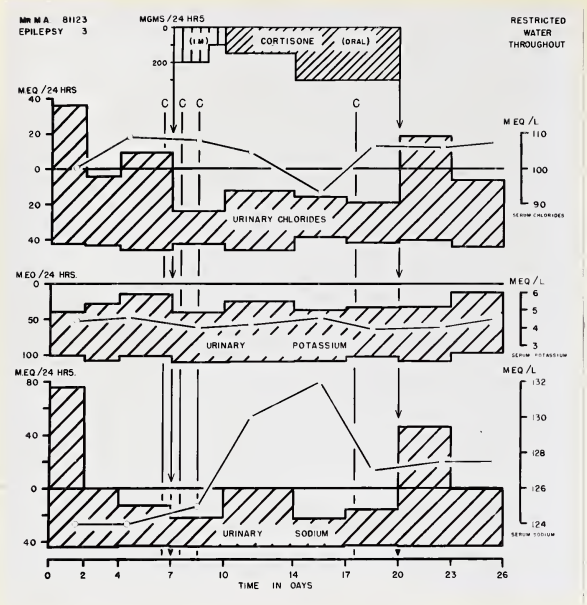


Figure 34. Metabolic data on Mr. M. A. #81123 with Idiopathic Epilepsy to show the effect of Cortisone.

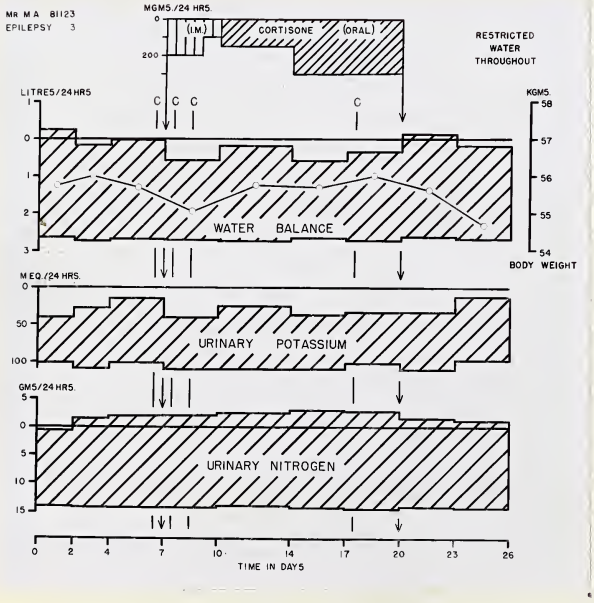


Figure 35. Idiopathic Epilepsy #81123. Metabolic data showing the effect of cortisone on nitrogen, potassium and water balances.

the sixteenth day of therapy. A pronounced drop was noted three days later when the serum sodium was 128 meq./l. and the level remained unchanged until discharge.

ii. Chloride Balance (Fig. 34).

In most respects the chloride balance followed the trends indicated by the sodium balance. During the first two days of the control, there was a negative balance of about 38 meq./l, following which the urinary output was diminished resulting in a slightly positive balance for two days. Prior to beginning therapy there was a slight diuresis of chlorides. Cortisone resulted in a prompt and pronounced retention of the element, which persisted until oral cortisone (150 mgm. q.d.) was begun. At this time the urinary output increased and the positive balance was about 12 meq. per day. The retention became more pronounced when the cortisone dose was doubled and continued until cessation of therapy, at which time there was a prompt diuresis of chlorides for three days. The patient was in balance prior to discharge.

Serum chloride values remained within the normal range throughout the entire study. During cortisone therapy the values dropped to 90 meq./l at which time there was a marked urinary retention of the element. There was no other pronounced changes observed in the serum chloride levels.

iii. Potassium Balance (Fig. 34).

A persistant retention of potassium was noted during this study. Initially there was retention of potassium of about 40 meq. per day, but during the remainder of the control the urinary output of potassium increased resulting in a slightly diminished positive balance.

Cortisone induced a greater retention of the element when administered intramuscularly than during the first four days of oral therapy. However, the increased oral dosage caused a slightly greater positive balance, which persisted until three days after cessation of therapy. During the three days prior to discharge the retention of potassium was minimal amounting to about 12 meq. per day.

Serum potassium values remained unchanged and within the normal range throughout the study.

(b) The Effect of Cortisone on Nitrogen and Water Balances, and Weight (Fig. 35).

The patient was in nitrogen balance during the first two days of the control following which there was a persistent negative balance throughout the duration of the investigation. There was a slight increase in the urinary output of nitrogen during cortisone, and following cessation of therapy the urinary output diminished resulting in a negative balance of about 1 gm. per day.

Fluid balance established early in the control was upset by cortisone (I.M.), which resulted in a retention of water (500 c.c. per day). The change to oral cortisone resulted in a decreased positive balance of only 150 c.c. per day. Doubling the dose produced a slightly greater retention of water, following which cessation of therapy caused a slight diuresis of about 100 c.c. per day for three days and then a slight retention of similar amounts of water for three days.

The body weight rose slightly during the control to 56 kg., and after cortisone was begun there was a drop of about 1 kg. during the first three days. This was followed by a gradual increase in body weight until

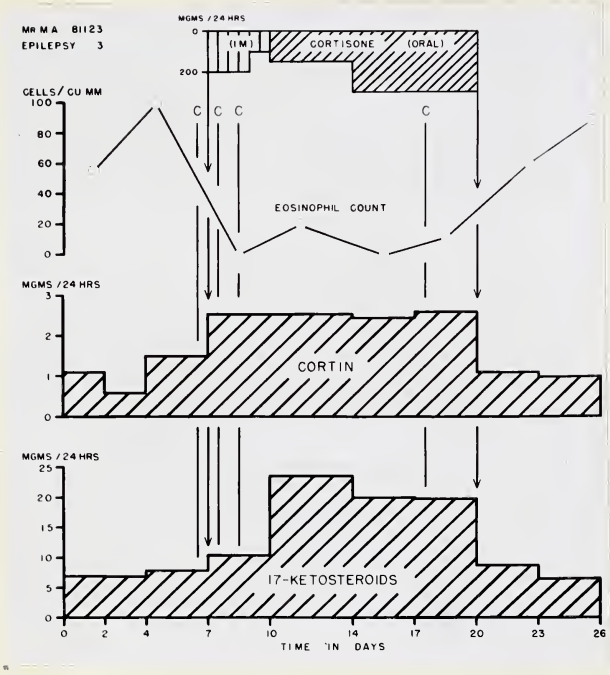


Figure 36. Idiopathic Epilepsy #81123.
Chart showing the effect of Cortisone on the urinary output of cortin and 17-ketosteroids, and circulating eosinophils.

cessation of therapy, which resulted in a fairly prompt loss of about 1.5 kg.

(c) The Effect of Cortisone on the Urinary Output of Cortin and 17-Ketosteroids, and Circulating Eosinophil Levels (Fig. 36).

Cortisone resulted in a very slight elevation of the 17-Ketosteroids during the first three days of therapy, after which the urinary excretion was increased from a pre-treatment mean of 9 mgm. per twenty-four hours to 25 mgm. per twenty-four hours. Following cessation of therapy there was a prompt decrease in the urinary excretion of 17-ketosteroids.

The urinary output of cortin on the other hand showed a more prompt response to cortisone therapy rising from a pre-treatment mean of 1.3 mgm. per twenty-four hours to 2.6 mgm. per twenty-four hours, during the first three days of therapy. There was also a prompt fall in corticoid excretion following treatment. Changes in the route of administration or the dosage produced no significant changes in the cortin level, while the 17-ketosteroids showed the most pronounced increase during therapy with oral cortisone (150 mgm. q.d.). Urinary excretion of 17-ketosteroids was diminished slightly when the dosage was doubled during the last six days of therapy.

The eosinophils showed a characteristic drop from a pre-treatment mean of 80 cells/cu. mm. to a mean of 20 cells/cu. mm. during the administration of cortisone. Following therapy the level of circulating eosinophils again rose to pre-treatment levels.

(d) The Effect of Cortisone on the Electroencephalogram.

The improvement observed after instituting the low water intake was not maintained during treatment with cortisone. There was a general-

ized increase in abnormal electrical activity (Fig. 41 Tr. 33 & 34) and high voltage delta waves (notably 4 per second reaching 90 microvolts) were seen appearing frequently in the alpha rhythm. The abnormality was diffuse, but remained more localized in the right occipital region (Fig. 42 Tr. 35 & 36).

(e) Other Effects of Cortisone.

Accompanying the electroencephalographic changes were some changes in personality. The patient became slightly more paranoid, although at times he exhibited a greater sense of well being than usual. He was frequently bothered by headaches and complained for some time of pain in the hips, although oral cortisone was used throughout the greater part of the experiment.

(3) Comments.

Urinary retention of sodium and chlorides has been observed by other workers (147). However, the fact that cortisone is a salt-retaining hormone in the absence of any other adrenal hormones (345) would suggest that there may be a deficiency of DOCA-like substances in this patient. The fact that there was persistent retention of potassium throughout the entire experiment would seem to substantiate this hypothesis, for DOCA if present would cause retention of sodium and a diuresis of potassium rather than a retention of the element like that observed.

Loss of urinary nitrogen and potassium usually follows the administration of cortisone (153). The slight loss of nitrogen in this case was similar to that observed in debilitated individuals. However, it was not paralleled by a corresponding increase in urinary potassium. Body weight was noted to diminish slightly after the initial treatment

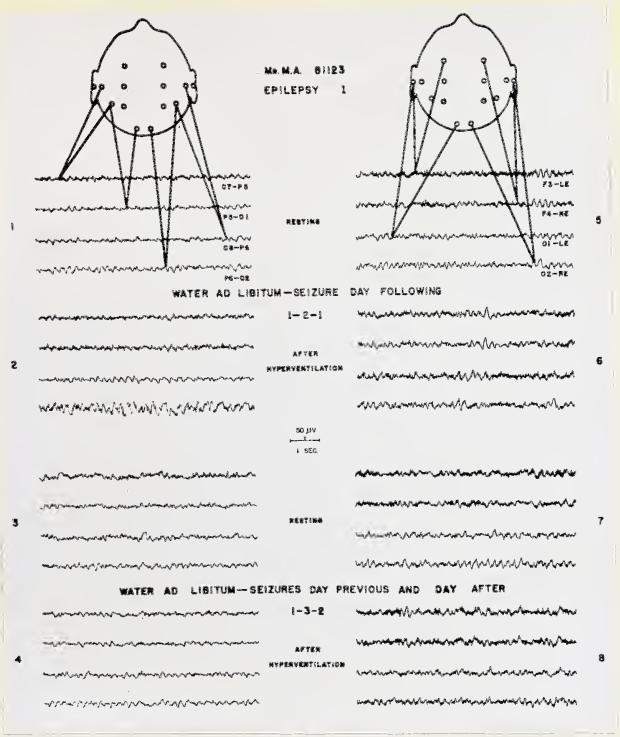


Figure 37.

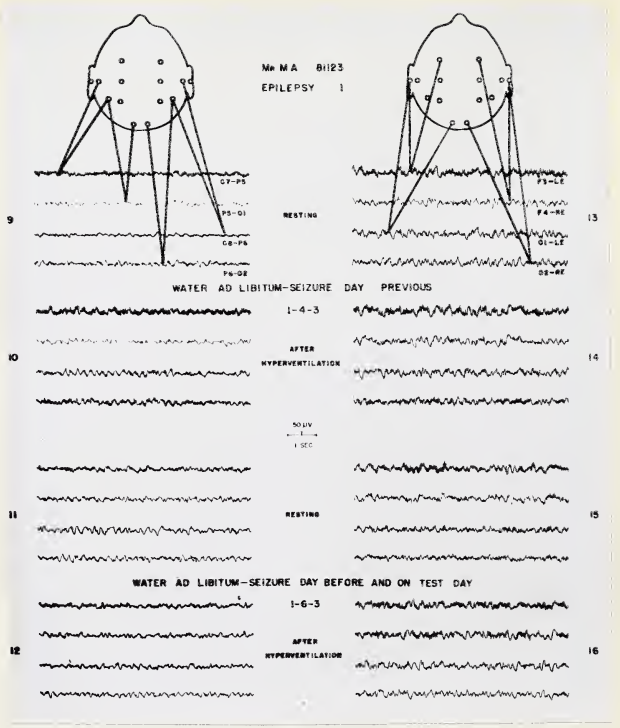


Figure 38.

Idiopathic Epilepsy #81123. Electroencephalographic picture with no therapy and water ad libitum.

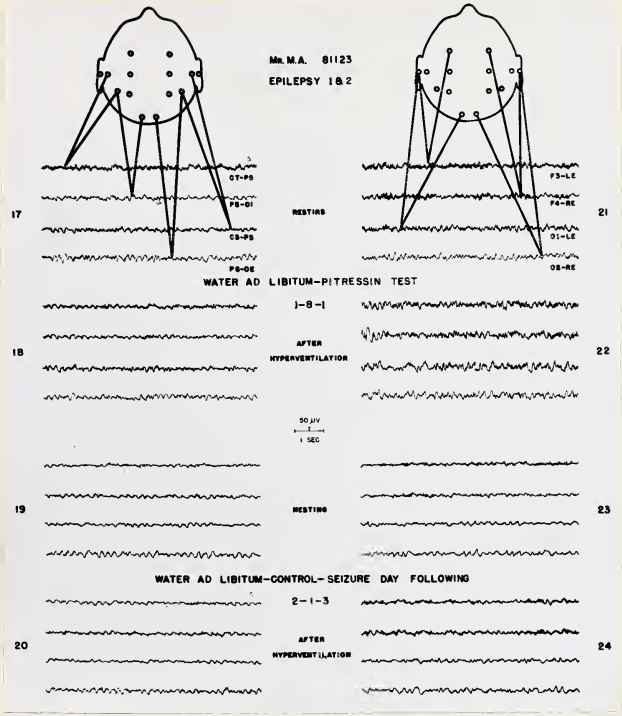


Figure 39.

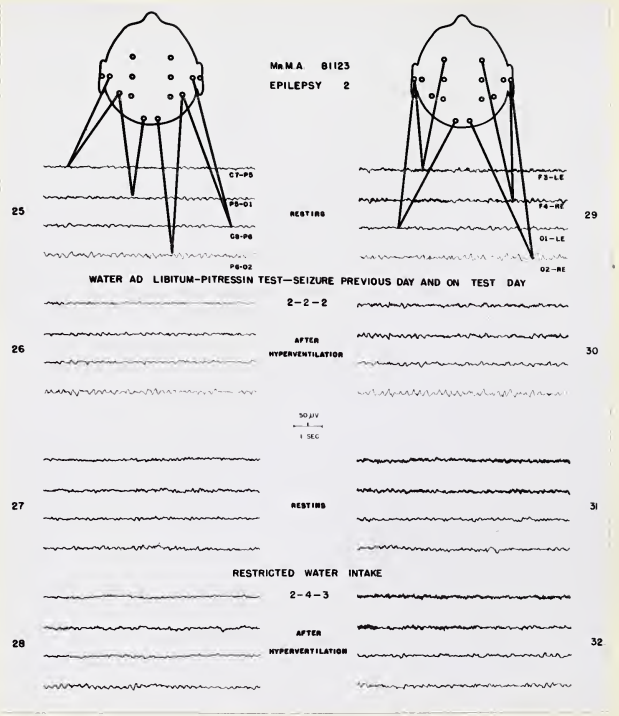


Figure 40.

Idiopathic Epilepsy #81123. The effect of Pitressin and restricted water intake on the electroencephalogram.

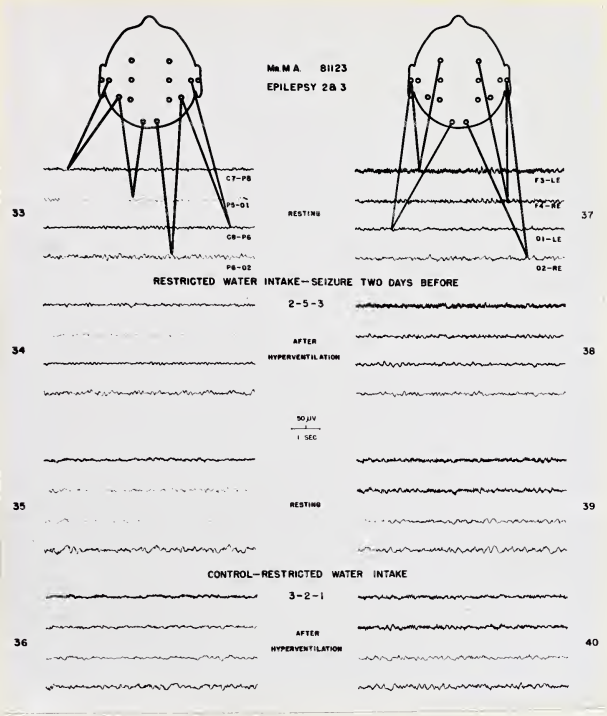


Figure 41.

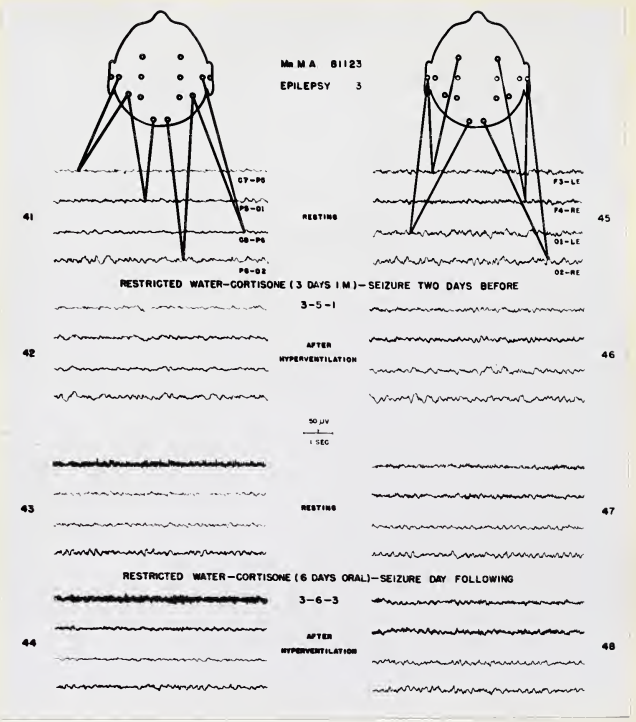


Figure 42.

Idiopathic Epilepsy #81123. The effect of restricted water intake and Cortisone on the electroencephalogram.

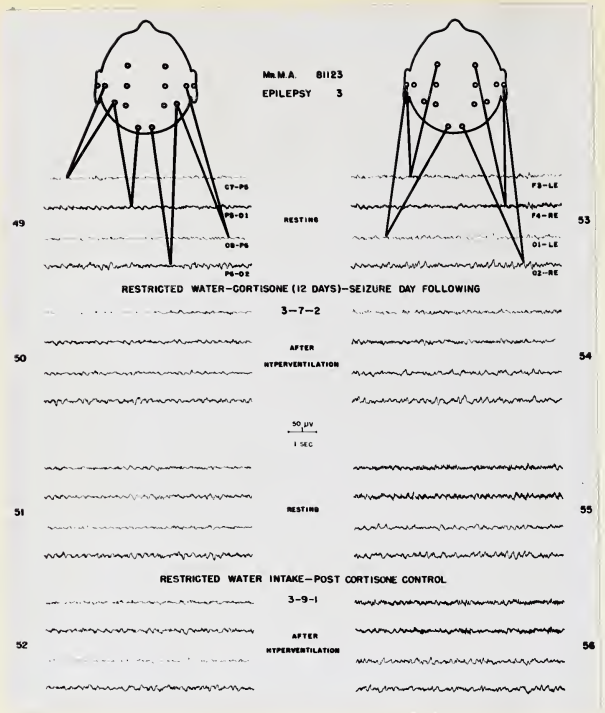


Figure 43. Idiopathic Epilepsy #81123.
The effect of Cortisone on the electroencephalogram.

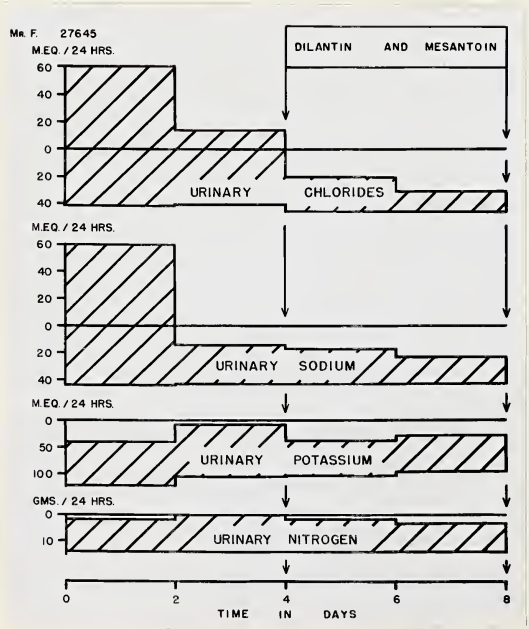


Figure 44. Chronic rheumatoid arthritis #27645. The effect of Dilantin and Mesantin on the sodium, potassium, chloride and nitrogen balances.

with intramuscular cortisone, presumably because of the slightly increased output of nitrogen. With the retention of water that occurred later in the treatment period, there was a gradual increase in weight even though loss of urinary nitrogen continued. Following cessation of therapy and in spite of the diminished nitrogen loss, there was a diuresis of water, which accounted for the loss of weight.

The changes in the urinary output of corticoids and 17-ketosteroids observed during therapy with cortisone were characteristic (52)(147), although it was noted that the rise in 17-ketosteroids was more pronounced following oral administration of the hormone. This may have been due to the more rapid rate of absorption of the oral preparation. The fall in eosinophils which occurred has been described (147).

More high voltage, slow-wave electrical activity appeared in the electroencephalogram during cortisone therapy. Similar observations have been reported (413) with both ACTH and cortisone, although some investigators (126)(405) have noted an improvement of the electroencephalogram following treatment with cortisone.

The possibility of abscess development made it desirable to change the route of administration of the drug in this case. It was found that the oral route required about twice the dose (411)(412) that was needed intramuscularly to produce responses of equal magnitude.

The persistant retention of potassium observed throughout all phases of this study proved the most outstanding feature of the case des-

cribed. Since the patient first entered hospital for investigation it is estimated that he has retained approximately 270 grams of potassium with no ill effects. An electrocardiogram failed to reveal any evidence of disordered potassium metabolism, although there was a slight bradycardia.

That such a massive retention could possibly occur without any marked physiological changes seemed most improbable. However, to gain some knowledge as to the fate of the potassium, a series of preliminary tests were carried out. A determination of intracellular potassium performed upon hemolyzed red blood cells which had been separated from the plasma by centrifugation was normal (93 meq./l) (414), and suggested that the element was not being retained in the intracellular spaces. As the serum potassium levels had been normal throughout the study, it was thought that the ion was being excreted in some abnormal manner and in excessive amounts. It was postulated that excessive amounts were being lost in the sweat or feces. However, flame photometric studies (337) revealed the excretion by these channels to be normal. Thermal sweat contained 49 meq./l of potassium, and the fecal loss 11.4 meq. per day, both of which are normal losses (414).

The possibility was entertained that the calculated diet figures were in error, but determinations by flame photometry indicated a dietary intake of 84.2 meq./ day for the test day, as compared with the calculated intake of 87.4 meq. per day.

The retention of potassium next was thought to be linked in some way with the anticonvulsive therapy of the patient. In order to test this hypothesis, a preliminary balance study was carried out on a non-epileptic patient.

The patient, Mr. F., age 67, was afflicted with chronic rheumatoid arthritis and had been on no therapy for a considerable time prior to the test. He was fed the same diet as was being given to the epileptic patient under observation. Following a four day control interval, anticonvulsive therapy identical to that received by the epileptic was administered for an additional four days.

During the first two days of the control there was a retention of potassium (Fig. 44), following which the patient was in potassium balance until the anticonvulsant therapy was begun. The retention of potassium was similar to that observed in the case of the epileptic studied and persisted until cessation of therapy.

While the data presented is not conclusive, they suggest that the mechanism responsible for the observed retention of potassium is mediated through the anticonvulsive therapy. It has been recognized that patients and experimental animals depleted of potassium become alkalotic (344) and that alkalosis results in lowered convulsive thresholds (377) (387). It is suggested that the anticonvulsives induce a retention of potassium and an acidosis which is known to elevate the seizure threshold (387). Much more work along this line is required to account for such contrary facts, as the protection against convulsions afforded by low potassium diets given to rate (387) and the beneficial results obtained in epilepsy with DOCA therapy (377)(388), which is thought to act by reducing brain potassium (403). Further it is suggested that future studies should include the study of the effects of DOCA on an epileptic patient loaded with potassium salts. Certainly in the light of the poor results obtained with cortisone in this case, a trial with DOCA is warranted.

Apparently cortisone acted like pitressin to produce no clinical or electroencephalographic improvement, although it was reported to be three times more effective in protecting animals against water intoxication (385).

(h) Summary.

A case of epilepsy treated with cortisone is described. By means of a pitressin test a polyuria, at first attributed to inadequate production of anti-diuretic substance (diabetes insipidus), was found to result from a habitual intake of excessive amounts of water.

Pitressin administration to this patient resulted in water retention, a diminished urine volume with increased specific gravity, a diuresis of sodium, increased weakness and an elevated blood pressure. The effects on chloride and nitrogen excretion were variable, and no changes in potassium balance, urinary output of cortin and 17-ketosteroids, or circulating eosinophil levels were observed.

Clinically a diminished water intake produced no change in the frequency of the seizures, but they were much less severe, and the electroencephalogram was significantly improved. Lowered chemocorticoid excretion and gradually increasing urinary potassium and sodium outputs were observed following the lowered water intake. No change in the circulating eosinophil level was noted.

The metabolic response to cortisone administration were normal, although no electroencephalographic or clinical improvement was observed. There was retention of sodium, potassium, chlorides and water, a slight diuresis of nitrogen, increased urinary cortin and 17-ketosteroid output, and a depression of the circulating eosinophil levels.

It is estimated throughout the entire study 270 gms. of potassium were retained. Preliminary studies suggest that the retention of the element was caused by the anticonvulsives used by the patient. It is suggested that this phenomenon may be linked with the mechanism of action of the anticonvulsive drugs.

It is suggested that DOCA would be beneficial in this case because cortisone and pitressin acted in a similar manner to slightly increase the electroencephalographic abnormalities. Future observation of the effect of potassium salts in this case with and without DOCA may be of interest.

F. A Comparison of the Metabolic Effects of ACTH and Cortisone.

I. Sodium Balance.

Cortisone was observed to produce a diuresis of sodium when administered in relatively low doses, but when used in high dosage (300 mgm. per twenty-four hours) in a single case, a retention of the element occurred. ACTH also produced a diuresis of sodium, which occurred following a slight retention of the element which was observed during therapy.

	Sodium Meq./Day			Potassium Meq./Day			Treatment
	Control	Therapy	Control	Control	Therapy	Control	
Cushing's	+36.4	+ 2.09	-13.12	+11.13	- 4.62	+16.49	Cortisone
Adreno-genital	- 8.35	-34.34	-54.74	+ 8.82	+ 3.38	+ 0.95	Cortisone
Adreno-genital	+ 1.26	-10.07	+12.9	+17.97	+18.03	+ 8.98	ACTH
Allergic Urticaria	+ 5.23	+ 6.93	- 2.9	+24.15	+14.20	+17.20	ACTH
Epilepsy	-20.74	+15.56	-22.44	+27.98	+34.31	+22.09	Cortisone

Table I. Comparison of the average daily sodium and potassium Balances occuring before, during and after therapy with ACTH or Cortisone.

II. Potassium Balance.

Potassium loss followed therapy with cortisone in two of the three cases studied. One case, however, receiving 300 mgm. per day of cortisone showed a retention of potassium. ACTH administration was followed by a loss of potassium in one case, and a slight retention of the element occurred in another instance, although in both cases the dosage was the same.

III. Chloride Balance.

A diuresis of chlorides was observed to follow administration of ACTH in both the cases described, whereas only two of three cases showed a similar diuresis of chlorides when treated with cortisone. Again the large dose of cortisone used was believed to be the factor resulting in the retention of the element observed in the other case.

	Chlorides Meq./Day			Nitrogen Gm./Day			Treatment
	Control	Therapy	Control	Control	Therapy	Control	
Cushing's	- 3.72	- 8.68	-31.21	- 0.05	-1.45	-3.9	Cortisone
Adreno-genital	-12.2	-41.0	-61.55	- 0.9	-5.03	-5.3	Cortisone
Adreno-genital	-12.08	-31.31	-30.17	+ 1.27	+ .45	+ .43	ACTH
Allergic Urticaria	-13.30	-17.05	-30.88	+ .74	-1.08	+0.5	ACTH
Epilepsy	-13.77	+17.86	- 5.71	- 0.91	-2.58	-1.43	Cortisone

Table 2. Comparison of the average daily chloride and nitrogen balances occurring before, during and after therapy with ACTH or Cortisone.

IV. Nitrogen Balance.

Nitrogen loss was consistently observed to follow the administration of both cortisone and ACTH in all of the cases reported.

V. Eosinophil Response.

ACTH and cortisone depressed the circulating eosinophil levels in all cases except one. In this case the dosage of ACTH (25 mgm. b.i.d.) was believed to be inadequate, although the possibility is entertained that there was a transitory fall in the eosinophils, which remained undetected due to the length of time between determinations.

	Eosinophils Cells/cu.mm.			17-Ketosteroid Mg./24 Hr.			Treatment
	Control	Therapy	Control	Control	Therapy	Control	
Cushing's	110	27	33	13.9	23.9	16.76	Cortisone
Adreno-genital	165	37	55	77.1	27.6	11.9	Cortisone
Adreno-genital	150	180	330	45.1	48.4	39.8	ACTH
Allergic Urticaria	160	32	136	8.81	11.5	7.6	ACTH
Epilepsy	77	8	74	7.19	18.4	7.55	Cortisone

Table 3. Comparison of the average daily urinary output of 17-ketosteroids, and the mean daily level of circulating eosinophils, occuring before, during and after therapy with ACTH and Cortisone.

VI. Urinary Output of 17-Ketosteroids.

Both ACTH and cortisone resulted in a rise in the urinary output of 17-ketosteroids, except in the case of the adrenogenital syndrome, which was treated with cortisone. A prompt and prolonged fall of 17-ketosteroid excretion was seen in this case.

VII Urinary Output of Cortin.

The urinary excretion of cortin was elevated in all cases studied, presumably because ACTH stimulated the production of increased amounts of the 11-oxysteroids, which hormones are reflected by the cortin

excretion. Administration of exogenous 11-oxysteroids (cortisone) of course increased the urinary output of cortin.

	Cortin Mgm./24 Hrs.			Blood Pressure mm./hg.			Treat-ment
	Control	Therapy	Control	Control	Therapy	Control	
Cushing's	1.69	4.97	3.69	132/91	138/89	158/102	Cortisone
Adreno-genital	1.02	2.44	1.32	125/73	126/75	124/74	Cortisone
Adreno-genital	0.64	0.70	0.63	101/69	112/73	111/77	ACTH
Allergic Urticaria	0.83	1.52	0.57	112/79	112/72	109/75	ACTH
Epilepsy	1.1	2.54	1.06	135/95	134/91	125/89	Cortisone

Table 4. Comparison of mean daily cortin and blood pressure determinations obtained before, during and after therapy with ACTH or cortisone.

VIII Blood Pressure.

The effects upon the blood pressure were variable. Two cases in this series showed an elevated blood pressure following therapy. Apparently both ACTH and cortisone are capable of elevating the blood pressure, although the mechanism of this response is not well understood at present.

	Urine Volume C.C.			Specific Gravity			Treat-ment
	Control	Therapy	Control	Control	Therapy	Control	
Cushing's	1070	1146	1240	1.017	1.017	1.018	Cortisone
Adreno-genital	1190	1317	1739	1.016	1.019	1.016	Cortisone
Adreno-genital	546	571	552	1.030	1.030	1.029	ACTH
Allergic Urticaria	1365	924	1310	1.014	1.021	1.014	ACTH
Epilepsy	1661	1244	1601	1.012	1.016	1.012	Cortisone

Table 5. Comparison of mean daily urine volume and specific gravity, before, during and after treatment with ACTH or cortisone.

Urine Volume and Specific Gravity.

The effects of ACTH and cortisone on the urine volume and specific gravity were also variable. In low dosage cortisone apparently causes an increase in urine output accompanied with no marked changes in specific gravity. High dosage of cortisone resulted in a retention of water that was coincident with an elevated specific gravity. ACTH resulted in a decreased urine volume in the case of allergic urticaria, whereas little change was noted in the other patient receiving similar therapy.

It was noted that the responses to ACTH and cortisone varied even though similar dosages of these substances were used. A dose, which was pharmacologic under certain conditions, was seen to be incapable of producing the same response at other times and in other patients. It has been suggested (415) that the wide range of responses observed is due to the varying needs of the tissue, which fluctuates with the activity and environment of the organism at the particular time of study. That the same hormone can induce retention or diuresis of sodium, chlorides or water; be anabolic or catabolic; or promote or depress glucose utilization can only be explained on the basis that the functional status of the individual cell is not static. It is obvious then in the light of these observations that no fixed amount of a hormone such as ACTH or Cortisone constitutes a physiological dose, and that the effects observed with their use are determined by conditions existing within the cell at the time of therapy. One would concur with Sayers (195) who points out that further studies of the adrenal hormones demand a wider application of such concepts concerning dose and response.

SUMMARY

1. The historical background concerning investigation of the physiology of the adrenal cortex was described.
2. A review and evaluation of some of the literature on the subject was presented.
3. The methods and procedure for performing metabolic and biochemical studies were outlined.
4. The results obtained from studies of patients with Cushing's Syndrome, Adrenogenital Syndrome, Allergic Urticaria and Idiopathic Epilepsy were presented.
5. The significance and possible explanation of some of the results observed were discussed. Probable lines of future investigation were indicated.
6. The metabolic effects of the adrenocorticotrophic hormone (ACTH) and cortisone were compared.

H - APPENDICES.

APPENDIX I.

Flame Photometry.

(a) Principle.

The principle of the flame photometer, which was devised to measure low concentrations of sodium and potassium in solution has been described by Barnes et al (416). The solution to be analysed is discharged through an atomizer in a fine mist into a mixing chamber, whence along with a combustable gas it is drawn into a flame. The light emitted by the excitation of the elements in the vaporized solution is conducted through an optical system to a photoelectric cell. By the use of lenses and appropriate filters, the light emission of particular elements may be isolated and measured. Light striking the photoelectric cell produces an electrical impulse, the magnitude of which is a function of the amount of the element in the sample. This electrical response may be utilized in two different ways for measurement purposes.

(1) The Absolute Method.

When using this method the current output of the photoelectric cell is measured directly by having it flow through a galvanometer, where the galvonmeter is used as a micro-ammeter. The method is fairly accurate under ideal circumstances, however serious errors may result from interfering substances in the sample, variations in flame temperature, or fluctuations in gas or air pressure.

(2) The Internal Standard Method.

The errors which may be encountered when using the Absolute Method may be eliminated in large measure by the use of a balance circuit.

A fixed quantity of Lithium, a substance not normally found in urine or serum is added to the sample. The output of a photoelectric cell activated by the Lithium is balanced against that of a cell responding only to the light emitted by either sodium or potassium. Most factors which influence the light intensity emitted by sodium or potassium will influence that emitted by Lithium in the same manner and to the same degree. In this method the galvanometer is used as a null instrument, and is returned to zero by the use of a potentiometer. The potentiometer reading, therefore, is a measure of the concentration of sodium or potassium in the solution, the actual concentration of which is obtained from a calibration curve.

(b) Apparatus.

During this investigation two flame photometers were used - a Barclay Flame Photometer and a Beckman DU Spectrophotometer equipped with a flame photometer accessory. In the former instrument three channels, each of which is fitted with appropriate lenses and filters, directs the light to three balanced photoelectric cells sensitive to sodium, potassium and lithium respectively. Such an arrangement permits the use of both the Absolute and Internal Standard Methods of analysis. The Beckman instrument on the other hand has but one photocell, and utilizes the principle of the Absolute Method of analysis. With the superior optical system of the spectrophotometer, however, most errors are eliminated as only the intensity of the spectral band characteristic of the element under observation is measured on the galvanometer. The accuracy of this machine, therefore, is comparable to that obtained with the Barclay instrument. The glass parts of both instruments were cleaned regularly with a detergent (Haemo-Sol) and sodium free distilled water. Filtered

air under pressure was used to vaporize the solutions, and the flame was fed by natural gas or propane of constant composition, which could be burned at any pressure by means of reducing valves on the instruments.

(c) Preparation of the Material.

Urine specimens were diluted one part to fifty of sodium free water, while the blood was first allowed to clot, centrifuged, and the serum diluted to one part in three hundred of the sodium free water. Dilution of specimens was necessary to bring the concentration of the elements being measured into the range which was optimum for accurate analysis.

(d) Procedure.

Calibration curves were constructed from readings (Table 6 for sample calibration data) obtained from a series of stock solutions containing sodium or potassium of various known concentrations. Four or more points were used to establish the slope of the curve. After stabilization of the curve, the unknown solution was introduced and the radings recorded. These were checked a second time, following which the standards closest to the unknown were re-checked. If the curve obtained during the calibration of the instrument remained unchanged, the reading for the unknown was accepted as valid, and the concentration of the element determined from the calibration curve.

The accuracy of the method compares favorably with that obtained from the most superior chemical methods (417).

Absolute Method				Internal Standard Method			
St. Sol.	Concentration PPM K	Na	Gal. Reading	St. Sol.	Concentration PPM Li	Na	Roten Reading
1	0	0	0	1	50	0	0
2	0	5	11	2	50	5	87
3	0	10	22	3	50	10	177
4	0	15	32	4	50	15	260
5	0	20	43	5	50	20	340

Table 6. Sample calibration data for both the Absolute Method and the Internal Standard Method.

(e) Difficulties Encountered During the Investigation Period.

When this series of investigations was begun, the Barclay Flame Photometer operating on natural gas was used for urine and serum sodium determinations only. Potassium determinations on this machine were very unsatisfactory due to the difficulty experienced in establishing reliable calibration curves. For that reason potassium determinations were performed using a Beckman DU Spectrophotometer equipped with a Flame Photometer Accessory. This arrangement existed throughout the investigation of Mrs. R. C. and Miss C. W., following which the Barclay Flame Photometer was returned to the manufacturer for repairs. Before it was returned another project was begun and the Beckman machine of necessity was used for all sodium and potassium determinations. Some months later, and too late to be of use in the remainder of the projects described, the Barclay Flame Photometer was returned. It became of interest, therefore, to determine whether the two instruments differed with respect to sodium values, so a small series of serum specimens were tested on both machines. Comparison of the results (Table 7) revealed no significant differences.

Material	Photometer		Absolute Change	Percent. Diff.	
	Beckman	Barclay			
Serum	154	153.9	0.1	.06	
Serum	143	147.3	4.3	3.0	
Serum	141	140.8	0.2	.01	

Table 7. Show comparison of values for serum sodium obtained on the Barclay and Beckman Flame Photometers.

As potassium determinations had been impossible previously, attempts were again made to calibrate the recently repaired machine with respect to that element. However, several weeks of experimentation revealed that the potassium cell was still defective, and it was returned to the manufacturer.

Erratic drifting of the galvanometer needle became increasingly apparent during the ensuing interval, during which attempts were made to calibrate the machine for determinations of sodium. It was decided that the "draft" was due to contamination of the air, so use of the machine was discontinued pending the availability of new space free of such contamination in which to install and operate it.

Throughout the course of the studies reported it was necessary to re-check several potassium and sodium determinations. Frozen specimens were used for this purpose, and there was found to be no changes in the values obtained in such repeat studies, which were attributable only to freezing. Data illustrating this point is presented below.

Specimen	Determi-nation	Before Freezing (Meq.).	After Freezing (Meq.)	Percent. Change	Number Days Frozen
Urine	K	77.7	75.1	3.4	65
Urine	K	64.1	66.6	3.9	49
Urine	K	80,3	78.7	2.0	103
Urine	K	74.3	77.5	4.3	98
Serum	K	4.8	4.5	6.2	103
Urine	Na	22.1	22.3	1.0	105
Urine	K	54.0	51.3	5.0	35
Urine	N	12.6	12.2	3.2	35
Urine	K	36.3	39.3	8.2	30
Urine	Na	46.38	42.0	9.5	35

Table 8. The effect of freezing on urinary and serum potassium determinations performed with the flame photometer.

APPENDIX II.

Factors Affecting the Determination of Urinary Cortin.

(a) Conditions of Storage.

Circumstances sometimes result in considerable delay before the extraction of a urine pool is begun. It was of interest, therefore, to determine the effects of storage under varied temperature conditions for relatively long periods of time prior to extraction.

A single urine specimen was used for the determinations described. Three aliquots (200 c.c.) were measured out and acidified to pH 1.7. The first and second specimens were stored at room temperature and at ice box temperature respectively for forty-eight hours prior to extraction. The third specimen was extracted immediately, and the cortin assays of all three extracts were determined in an identical manner.

The results (Table 9), although not statistically significant, indicate that refrigeration is necessary when conditions demand that the urine be stored prior to extraction.

Specimen	Time Stored	Temp.	Cortin Mgm./24 Hrs.
1	48 Hrs.	Room	0.89
2	48 Hrs.	Refrig.	1.11
3	Zero	-	1.24

Table 9. Table showing the effect of storage temperature on the determination of urinary cortin.

(b) The Effects of Freezing Prior to Extraction.

Sometimes it is desirable to repeat a cortin determination long after the specimen was collected. In such cases specimens which

were preserved by freezing are used. It was necessary, therefore, to determine the accuracy of such repeat determinations performed on frozen specimens.

Urine Spec.	3 Day Vol.	Mgm./24 Hrs. Before Freezing	Mgm./24 Hrs. After Freezing	Days Frozen	Actual Change	Percent. Change
1	1580 cc	1.30	1.42	175	+0.12	9
2	3300 "	.94	.74	170	- .20	21

Table 10. Table showing the effect of freezing on the determination of Urinary Cortin.

The data presented indicates that although there may be some change in the values obtained after freezing, such are not significant in the light of the experimental error of the method itself.

Appendix III

Tables of Metabolic Data

Cushing's Syndrome
Mrs. R. C. #96690

TABLE I (A)

URINARY BALANCE DATA

N.B. All values shown are average values for each three day period.

	SODIUM (Gms.)			POTASSIUM (Gms.)			CHLORIDES (GMs.)			NITROGEN (Gms.)			
3 DAY PERIOD	IN	OUT	BAL.	IN	OUT	BAL.	IN	OUT	BAL.	IN	OUT	BAL.	TREATMENT
1	2.766	2.9	- .134	3.930	3.26	+.67	4.183	4.76	- .577	13.0	12.4	+ .6	Control
2	2.499	1.69	+1.809	2.929	2.73	+.199	3.701	2.86	+ .841	11.2	11.9	- .7	Control
3	2.474	3.15	- .676	2.773	3.33	-.557	3.648	4.98	-1.332	11.2	11.9	- .7	Cortisone
4	2.612	1.84	+ .772	3.287	3.1	+.187	3.885	3.17	+ .715	11.2	13.4	-2.2	200 mgm. q.d.
5	2.485	3.05	- .565	3.272	2.6	+.672	3.737	5.12	-1.383	11.2	14.8	-3.6	Control
6	2.608	3.0	- .392	3.244	2.8	+.444	3.897	5.0	-1.103	11.3	15.4	-4.1	Control
7	2.525	2.93	- .405	3.234	2.43	+.804	3.761	4.71	- .949	11.2	14.9	-3.7	Control
8	2.655	2.5	+ .155	3.054	2.4	+.654	3.912	3.8	+ .112	11.3	14.7	-3.4	Control
Ave.													
St.Dev.													

TABLE I (B)

3 DAY PERIOD	EOSIN.	B.P.	Hb.	HMT	WBC	CO_2 Meq./l	Cl. Meq./l	Na Meq./l	K Meq./l	SUG. Mg.%	T.P. Gms.	A/G RATIO	Treat-ment
1	88	137/97	14.6	50.	5600	24.5	109.2	142.2	5.5	80	6.7	4.0/2.7	Control
2	132	127/86	15.0	49	6200	24.	110.5	151.3	3.8	79	6.0	3.9/2.1	Control
3	33	131/88	15.8	49	13000	26.	111.4	150.0	2.8	94	6.2	4.0/2.2	Cortisone
4	22	145/90	13.4	47	7370	25.	106.2	142.2	5.22	97	7.1	4.4/2.7	200 mgm. q.d.
5	22	159/102	15.0	43	5580	25.	110.7	140.9	4.33	91	5.9	3.5/2.4	Control
6	33	162/101	15.4	44	8500	25.5	107.9	142.2	4.22	88	6.2	3.8/2.4	Control
7	16	162/107	15.4	49	8500	25.3	105.5	146.	5.94	78	6.0	3.7/2.3	Control
8	60	150/99	14.6	49	8800	25.	110.7	142.2	4.45	83	6.3	4.2/2.1	Control
Av.	17		14.9	47.5	7944	25.04				86.3	6.3		
St.Dev.			± .69	±2.45	± 72	± .563				± 6.78	± .281		

BIOCHEMICAL DATA
SHOWING EFFECTS OF CORTISONE

N.B. All values shown are average values for each three day period.

Mrs. R.C. # 96690

Cushing's Syndrome Cont'd.

TRBLE I (C)

3 DAY PERIOD	URINE VOL.	SPEC. GR.	CREAT-ININE	WEIGHT Kgs.	Mgm. 17-K.S.	Mgm. CORTIN	TREATMENT	
1	1198	1.017	1.14	61.20	14.3	1.41	Control	
2	943	1.017	1.04	61.10	13.5	1.98	Control	
3	1420	1.015	1.17	61.5	24.7	4.47	Cortisone	
4	872	1.020	1.07	61.40	23.1	5.47	200 mgm. q.d.	
5	1293	1.017	1.12	60.90	19.8	4.71	Control	
6	1447	1.017	1.01	59.90	18.7	4.71	Control	
7	970	1.022	1.08	59.80	14.5	2.93	Control	
8	1253	1.016	.88	58.7	14.03	2.41	Control	
Average			1.06					
St. Dev.			±0.093					

BIOCHEMICAL DATA SHOWING EFFECTS
OF CORTISONE

N.B. All values shown are average daily values for each three day period.

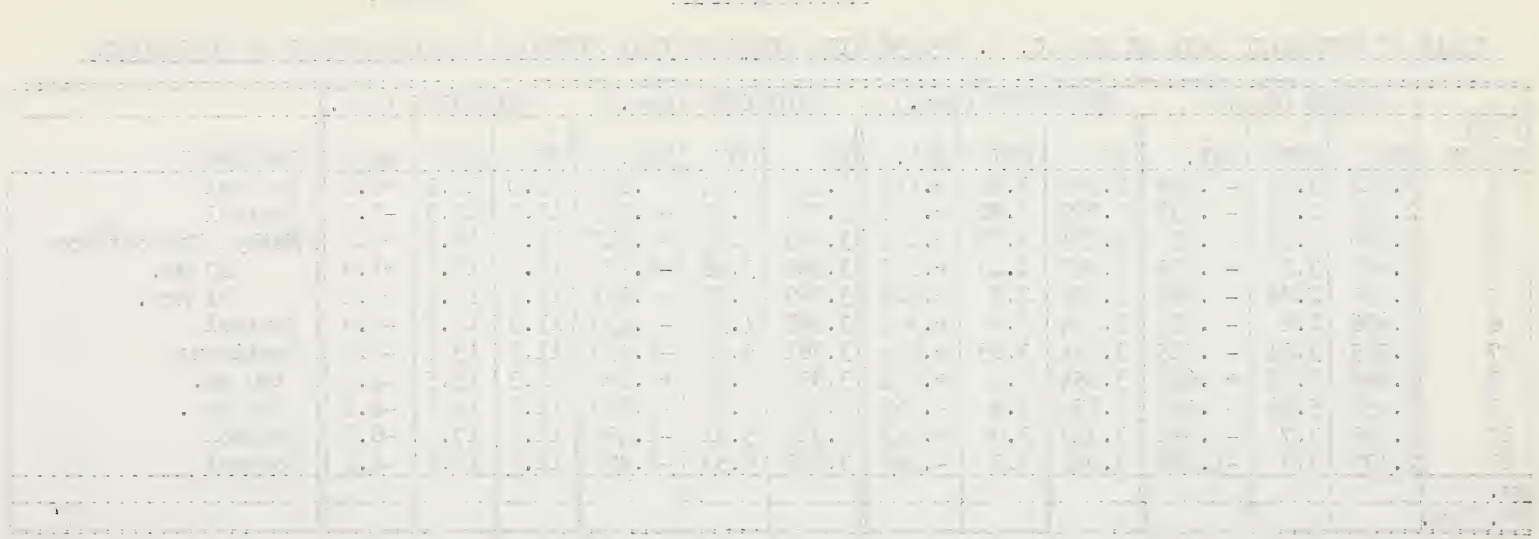
TABLE II (A)

TABLE OF METABOLIC DATA ON MISS C. W. #96696 WITH ADRENOGENITAL SYNDROME SHOWING EFFECT OF CORTISONE.

	SODIUM (Gms.)			POTASSIUM (Gms.)			CHLORIDES (Gms.)			NITROGEN (Gms.)			
3 DAY PERIOD	IN	OUT	BAL.	IN	OUT	BAL.	IN	OUT	BAL.	IN	OUT	BAL.	TREATMENT
1	2.912	3.02	- .108	3.907	3.46	+.447	4.411	5.04	- .629	13.0	12.3	+0.7	Control
2	2.499	2.73	- .231	2.929	2.80	+.129	3.701	4.55	- .849	11.2	12.3	-1.1	Control
3	2.460	2.93	- .47	2.834	2.70	+.134	3.623	4.44	- .817	11.2	10.8	+0.4	Methyl Testosterone
4	2.625	3.1	- .475	3.287	2.43	+.857	3.906	5.08	-1.174	11.2	10.2	+1.0	40 Mg.
5	2.495	2.89	- .395	3.326	2.8	+.526	3.789	4.72	- .931	11.2	11.0	+0.2	/24 Hrs.
6	2.608	2.8	- .192	3.244	2.9	+.344	3.897	4.33	- .433	11.3	12.2	-0.9	Control
7	2.525	3.04	- .515	3.234	3.03	+.204	3.761	5.22	-1.459	11.2	13.7	-2.5	Cortisone
8	2.668	2.02	+ .648	3.054	2.4	+.654	3.932	3.54	+ .392	11.3	15.5	-4.2	100 mg.
9	2.551	5.06	-2.509	3.138	3.6	-.462	3.891	7.19	-3.299	11.2	19.6	-8.4	/24 Hrs.
10	2.609	3.7	-1.091	3.343	3.0	+.343	3.912	5.41	-1.498	11.2	17.4	-6.2	Control
11	2.472	3.9	-1.428	3.031	3.3	-.269	3.658	6.53	-2.872	11.2	15.6	-4.4	Control
Av.													
St. Dev.													

TABLE II (B)

	SERUM												
3 DAY PERIOD	EOSIN.	B.P.	Hb.	HMT	WBC	CO_2 Meq./l	Cl Meq./l	Na Meq./l	K Meq./l	SUG. Mg.%	T.P. Gms.	A/G RATIO	TREATMENT
1	165	122/81	15.4	48	6350	26.1	103	143.5	4.8	84	8.0	4.8/3.2	Control
2	275	126/78	16.2	47	6800	26.	107	150.	3.32	80	7.7	4.8/2.9	Control
3	231	125/76	15.8	48	7700	28.4	107	153.9	3.75	79	7.6	4.8/2.8	Methyl Tes-
4	209	125/78	14.6	48	6500	26.7	104.4	144.7	4.76	87	7.7	5.0/2.7	osterone
5	220	123/75	14.6	45	5040	26.1	108.1	153.9	4.53	86	7.5	5.0/2.5	40 mg./24 Hrs.
6	165	125/73	15.4	47	5010	26.7	105.3	143.4	4.36	82	7.4	4.7/2.7	Control
7	39	126/74	14.6	50	11200	25.6	99.3	147.3	5.13	87	7.8	4.8/3.0	Cortisone
8	33	129/77	15.8	53	11350	25.4	101.	143.4	4.48	98	8.4	5.0/3.4	100 mg.
9	38	123/73	13.8	50	10400	27.2	101.	146.0	4.60	87	6.9	4.2/2.7	/24 Hrs.
10	55	120/76	15.	46	12400	28.	102.	144.7	4.25	87	7.7	4.6/3.1	Control
11	55	127/71	16.2	55	6300	28.	102.6	143.4	4.25	87	7.3	4.6/2.7	Control
Av.			15.2	48.8	8095	26.8				85.82	7.63		
St.Dev.			± 0.727	±2.85	±81.6	± .962				±4.80	± .385		



Adrenogenital Syndrome

TABLE II (C)

N.B. All values shown are average daily values for each three day period.

Miss C. W. #~~96696~~ cont'd.

3 DAY PERIOD	URINE VOL.	SPECIFIC GRAVITY	CREAT-ININE	WEIGHT Kgs.	17 K.S. Mgm.	CORTIN Mgm.	TREATMENT	
1	1512	1.013	1.38	102.0	97.0	1.52	Control	
2	1831	1.011	1.41	101.8	79.8	1.53	Control	
3	1830	1.008	1.16	101.5	108.3	0.88	Methyl Testosterone	
4	1397	1.012	1.46	102.	87.7	0.99	40 Mg.	
5	1413	1.013	1.69	102.	86.8	1.02	/24 Hrs.	
6	1190	1.016	1.47	101.8	77.1	1.02	Control	
7	1163	1.019	1.97	101.3	46.0	2.01	Cortisone	
8	990	1.021	1.51	101.5	19.3	2.35	100 Mg.	
9	1797	1.016	1.50	102.7	17.6	2.95	/24 Hrs.	
10	1683	1.017	1.43	101.2	13.8	2.28	Control	
11	1793	1.015	1.25	99.7	10.0	1.36	Control	
Av.			1.48					
St.Dev.			± 0.205					

BIOCHEMICAL DATA SHOWING THE EFFECTS OF CORTISONE

Diet: Carbo-hydrates 225 gms.
Proteins 70 gms.
Fat 80 gms.
Calories 1900.

TABLE III A
URINARY BALANCE DATA
SHOWING RESULTS OF ACTH

N.B. All results shown are average daily values for each three day period.

Adrenogenital Syndrome
Mr. R.C. #99205

	SODIUM Meq			POTASSIUM Meq			CHLORIDES Meq			NITROGEN Meq			
PERIOD	IN	OUT	BAL.	IN	OUT	BAL.	IN	OUT	BAL.	IN	OUT	BAL.	TREATMENT
1	59.39	42.0	+17.39	66.49	51.3	+15.18	53.32	67.5	-14.18	10.72	12.2	-1.48	Control
2	65.61	89.56	-23.95	71.18	88.45	-17.27	67.32	86.71	-19.39	11.80	14.9	-3.1	Control
3	88.49	79.7	+ 8.79	71.54	39.3	+32.24	77.75	73.5	+ 4.25	11.89	7.53	+4.36	m.t.
4	77.56	71.01	+ 6.55	77.89	48.7	+29.19	62.09	74.8	-12.21	11.84	9.66	+2.18	m.t.
5	76.26	72.97	+ 3.29	63.75	51.7	+12.05	66.02	75.49	- 9.47	11.84	10.6	+1.24	Control
6	72.21	72.97	-00.76	75.6	51.7	+23.9	60.8	75.49	-14.96	11.89	10.6	+1.29	Control
7	71.27	82.6	-11.33	71.77	49.6	+22.17	54.3	89.32	-35.02	11.84	11.5	+0.34	ACTH
8	71.48	80.3	- 8.82	79.7	65.8	+13.9	63.4	91.0	-27.6	11.85	11.3	+0.55	ACTH
9	78.45	69.5	+ 8.95	72.1	65.4	+ 6.7	56.2	108.5	-52.3	11.56	10.8	+0.76	Control
10	78.56	61.7	+16.86	84.86	73.59	+11.27	61.25	69.3	- 8.05	11.91	11.8	+0.11	Control

TABLE III B
BIOCHEMICAL DATA

N.B.-m.t. methyl testosterone

	SERUM				URINE							
PERIOD	Cl Meq./l	Na Meq./l	K Meq./l	B.P.	Kgs. WT.	Volume Urine	Sp. Gr.	Creat-	Mgm. 17-KS.	Mgm. Cortin	Eosin.	Treatment
1	105.5	152.6	5.84	104/68	32.6	526	1.029	.91	42.5	1.3	429	Control
2	106.2	152.6	5.4	100/62	32.1	725	1.029	1.21	51.8	.94	209	Control
3	109.7	144.7	5.0	98/59	32.18	543	1.029	1.02	40.1	.66	159	m.t.
4	106	144.7	4.62	101/63	32.36	515	1.030	.91	39.1	.56	187	m.t.
5	105.5	146.0	4.62	97/59	32.6	546	1.030	.95	45.1	.64	154	Control
6	110.9	153.9	4.32	105/66	32.1	546	1.030	.95	45.1	.64	146	Control
7	109.9	138.2	4.34	113/72	32.18	550	1.031	1.05	46.4	.66	180	ACTH
8	106.2	140.8	4.5	112/74	31.8	592	1.028	.90	50.4	.75	---	ACTH
9	108.1	139.5	4.5	112/78	31.8	542	1.029	.93	39.2	.67	330	Control
10	107.2	140.8	4.46	109/75	31.60	562	1.029	.92	40.5	.60		Control
Avg.	107.5	145.4	4.76	105/68	32.13	564	1.029	.98				
St. dev'n	±1.9	±5.54	±0.48		±0.32	±56.85	±.0008	±.091				

TABLE IV A

URINARY BALANCE DATA
SHOWING EFFECTS OF ACTH

Allergic Urticaria
Mrs. J.W. # 99254

N.B. All values shown are average values for each three day period. In period 3, the daily results are tabulated.

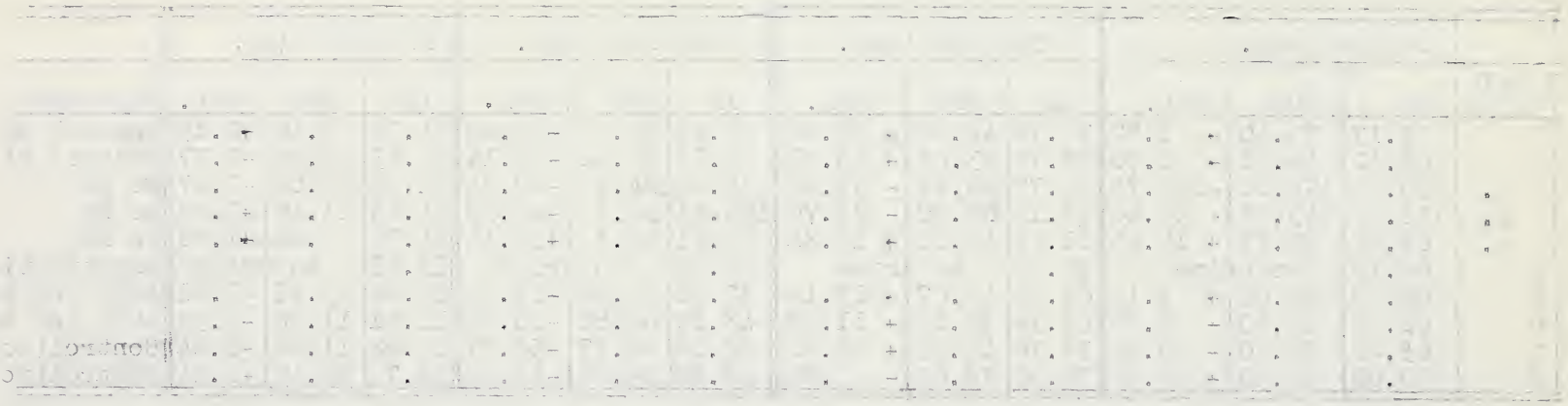
	SODIUM (Meq.)			POTASSIUM (Meq.)			CHLORIDE (Meq.)			NITROGEN (gm.)			
3 DAY PERIOD	IN	OUT	BAL.	IN	OUT	BAL.	IN	OUT	BAL.	IN	OUT	BAL.	TREATMENT
1	77.17	75.40	+ 1.77	77.38	44.40	+ 32.98	60.14	83.6	-23.46	11.35	9.10	+2.25	Control NA
2	68.12	59.42	+ 8.70	78.79	63.47	+ 15.32	53.18	56.32	- 3.14	11.83	12.60	-0.77	Control NA
3 a.	69.51	178.26	-108.75	65.77	99.35	- 33.58	55.46	124.5	-69.04	11.53	12.60	-1.07	No NA
b.	116.82	143.48	- 26.66	75.10	100.80	- 25.70	105.61	152.2	-46.59	11.65	11.40	+0.25	No NA
c.	68.82	52.17	+ 16.65	61.44	44.60	+ 16.84	59.61	46.5	+13.11	11.76	9.80	+1.96	No NA
4	66.19	no urine		76.20	no urine		54.20	no urine		11.65	no urine		Menstruation
5	68.19	63.04	+ 5.15	65.19	48.07	+ 17.12	57.58	70.94	-13.36	11.64	13.45	-1.81	ACTH (no NA)
6	62.32	53.60	+ 8.72	69.38	58.10	+ 11.28	48.85	69.60	-20.75	11.61	11.96	-0.35	ACTH (no NA)
7	65.40	94.80	- 29.40	78.30	42.20	+ 36.10	48.60	99.37	-50.77	11.62	11.86	-0.24	Control(no NA)
8	60.00	36.50	+ 23.50	76.90	78.60	- 1.70	48.80	59.80	-11.00	11.7	10.46	+1.24	Control(no NA)

TABLE IV B

BIOCHEMICAL DATA

N.B.-NA= neo-antergan

3 DAY PERIOD	CORTIN mgm.	17-K.S. mgm.	EOSIN	B.P.	WEIGHT Kgs.	URINE vol.	SPECIFIC GRAVITY	CREAT-ININE	TREATMENT
1	.72	9.3	198	114/79	75.09	1630	1.012	1.34	Control NA
2	.94	8.33	122	110/79	74.59	1100	1.015	1.31	Control NA
3 a.	1.12	7.4	154	111/78	74.68	1213	1.013	1.37	No NA
b.	1.07	8.1	128	111/78	74.68	1213	1.013	1.37	No NA
c.	.49	5.3	66	111/78	74.68	1213	1.013	1.37	No NA
4			143	111/73	74.82				Menstruation
5	1.16	10.5	33	109/69	73.75	830	1.024	1.35	ACTH (no NA)
6	1.89	12.5	30	116/76	74.21	1018	1.018	1.30	ACTH (no NA)
7	.39	6.9	198	108/73	73.55	1453	1.012	1.26	Control(noNA)
8	.76	8.4	209	109/76	72.61	1167	1.015	1.26	Control(no NA)
Average				111/75	74.16			1.31	
St.Dev.					± .763			±0.039	



Mr. M.A. #81123
Epilepsy I

TABLE V.A

URINARY BALANCE DATA
SHOWING EFFECTS OF PITRESSIN

N.B. All values shown are average values for each three day period.

3 DAY PERIOD	SODIUM (Meq.)			POTASSIUM (Meq.)			CHLORIDE (Meq.)			NITROGEN (Mem)			COMMENTS
	IN	OUT	BAL.	IN	OUT	BAL.	IN	OUT	BAL.	IN	OUT	BAL.	
1	44.15	88.69	-44.54	93.4	61.5	+31.9	37.56	106.8	-69.24	14.39	17.5	-3.1	
2	43.68	28.69	+14.99	115.79	77.7	+38.09	41.95	42.7	- .75	14.50	13.9	+0.6	Seizure (2)*
3	43.57	59.85	-16.28	95.76	64.1	+31.66	47.11	108.6	-61.49	14.42	14.8	-0.38	Seizure (1) (3)
4	43.47	57.24	-13.77	118.27	76.92	+41.35	48.51	69.2	-20.69	14.37	17.2	-2.8	Seizure (2)
5	42.4	81.45	-39.05	104.01	79.4	+24.6	39.07	104.4	-65.53	14.37	15.9	-1.5	
6	43.72	41.7	+ 2.02	117.24	71.8	+45.4	39.53	71.3	-31.77	14.32	16.9	-2.6	2 Seizures (2) (3)
7	43.52	56.8	-13.28	99.92	59.8	+40.1	38.06	85.3	-47.24	14.33	14.2	+ .1	
8	43.5	60.58	-17.08	111.01	65.8	+45.2	42.54	81.4	-39.86	14.33	12.7	+1.6	

*Italicized number indicates day of 3 day period.

TABLE V B

BIOCHEMICAL DATA
SHOWING EFFECTS OF PITRESSIN

PERIOD	SERUM					URINE							COMMENTS
	Cl Meq./l	Na Meq./l	K Meq./l	$C\Phi_2$ Meq./l	B.P.	Volume Urine	Sp. Gr.	Creat-	Kgm. Weight	Eosin	Mgm Cortin	Mgm. 17-KS.	
1	103.7	141	4.26	28	134/97	4167	1.006	1.43	57.37	110	1.69	7.08	
2	109	143	4.2	27	131/94	3570	1.006	1.40	56.8	176	1.46	7.8	Seizure (2)*
3	106	158	4.84	25.5	126/89	3530	1.005	1.41	57.18	77	1.57	6.7	Seizure (1) (3)
4	104.6	154	4.73	28	123/89	4050	1.005	1.49	56.92	110	1.29	8.5	Seizure (2)
5	107.8	156	4.84	28.3	119/86	4073	1.005	1.50	57.28	66	.67	9.8	
6	104.5	156	4.52	28	120/86	4168	1.004	1.27	57.05	88	.76	8.97	2 Seizure (2) (3)
7	106.4	156	4.1	26.3	120/84	3838	1.006	1.48	57.26	93	1.09	10.2	
8	103.6	146	4.6	26.7	122/88	3663	1.007	1.54	56.92	100	.54	9.7	
Avg.	105.7	151.3	4.51	27.2	124/89	3882	1.005	1.44	57.1	103	1.01	8.59	
St. Dev.				± .3		±252	±.001		± .57	± 3.1	± .60	±1.23	

TABLE V (C)

DAILY BALANCE DATA FOR PERIOD 6&8.

Mr. M.A. #81123
Epilepsy I

	SODIUM (Meq.)			POTASSIUM (Meq.)			CHLORIDE (Meq.)			NITROGEN (Gms.)			
DAILY PERIOD	IN	OUT	BAL.	IN	OUT	BAL.	IN	OUT	BAL.	IN	OUT	BAL.	COMMENTS
6a	43.86	46.52	- 2.66	107.8	71.8	+36.0	35.8	80.0	-44.2	14.3	15.1	- .8	
6b	43.85	46.95	-3.10	128.5	65.1	+63.4	36.5	57.3	-20.8	14.4	18.8	-4.4	2 Seizures.
6c	43.46	40.0	+ 3.46	115.5	61.0	+54.5	46.3	42.2	+ 4.1	14.2	15.5	-1.3	Seizure.
Mean	43.72	44.49	- .77	117.3	66.0	+51.3	39.5	59.8	-20.3	14.3	16.5	-2.2	
8a	43.48	104.78	-61.30	110.6	60.3	+50.3	37.70	96.8	-59.10	14.3	15.1	- .8	Pitressin
8b	43.52	20.87	+22.65	123.1	59.5	+63.6	46.17	50.84	- 4.67	14.3	16.2	-2.0	
8c	43.49	43.47	+ .02	99.1	67.2	+32.2	43.75	68.44	-24.69	14.4	12.6	+1.7	
Mean	43.59	56.37	-12.87	111.0	62.3	+48.7	42.54	72.03	-29.49	14.3	14.6	- .36	

Average Daily Diet:
Calories- 2100
CHO - 250 gms.
Protein - 90 gms.
Fat - 80 gms.

N.B. All values shown are average values for each three day period.

TABLE VI A

URINARY BALANCE DATA

Epilepsy II
Mr. M.A. # 81123

SHOWING EFFECTS OF DIMINISHED WATER INTAKE

		SODIUM (Meq.)			POTASSIUM (Meq.)			CHLORIDE (Meq.)			NITROGEN (gms.)			
PERIOD NUMBER	NUMBER OF DAYS	IN	OUT	BAL.	IN	OUT	BAL.	IN	OUT	BAL.	IN	OUT	BAL.	COMMENTS
1	3	43.34	31.45	+ 11.89	120.02	50.1	+70	42.96	77.2	-34.24	14.41	16.6	-2.2	
2	4	43.5	30.2	+ 13.3	110.3	61.5	+48.8	43.4	76.58	-33.18	14.46	16.25	-1.79	Seizure(1)(2)P3
3	3	43.5	12.5	+ 31.0	109.9	67.9	+42.	45.2	17.35	+27.8	14.37	15.2	- .83	Low water (3)
4	4	43.5	22.01	+21.49	103.8	74.35	+29.4	45.3	20.72	+24.58	14.4	14.43	- .03	
5	3	43.5	44.62	- 1.12	114.1	80.34	+33.8	43.1	31.04	+12.1	14.4	13.9	+ .5	Seizure(1)

N.B. P3 indicates Pitressin
1 Unit Q. 2H.

TABLE VI B

BIOCHEMICAL DATA

		SERUM	SERUM											
PERIOD NUMBER	NUMBER OF DAYS	Cl.	Na.	K.	CO_2 Meq.	B.P.	URINE vol.	SPECIFIC GRAVITY	CREAT-ININE	WT. kgs.	EOSIN	Mgm. CORTIN	17-KS Mgm.	COMMENTS
1	3	102.8	154	4.4	27	129/95	4517	1.006	1.43	57.5	99	.73	8.1	
2	4	105.6	155	4.4	22.9	132/101	4480	1.006	1.54	57.37	88	.64	7.6	Seizure(1)(2) P3
3	3	105.5	155	4.25	27	130/95	3383	1.007	1.40	57.45	66	.99	8.5	Low Water (3)
4	4	106.2	153	4.6	27	129/95	1515	1.014	1.45	57.23	77	.48	7.7	
5	3	107	153	4.8	27	133/97	1513	1.014	1.56	57.18	77	.44	8.0	Seizure(1)

TABLE VI C

DAILY BALANCE DATA FOR PERIOD 2.
SHOWING EFFECT OF PITRESSIN

Mr. M.A. #81123
Epilepsy II

	SODIUM(Meq.)			POTASSIUM(Meq.)			CHLORIDE(Meq.)			NITROGEN(gms.)			
DAILY PERIOD	IN	OUT	BAL.	IN	OUT	BAL.	IN	OUT	BAL.	IN	OUT	BAL.	COMMENTS
2 a.	43.63	25.65	+17.98	111.34	84.3	+27.04	42.54	88.94	-46.40	14.49	149	-.41	Seizure
2b.	43.52	64.78	-21.26	116.02	59.0	+57.02	41.03	58.37	-17.34	14.48	15.3	-.82	Seizure
2c.	43.47	17.83	+25.64	103.15	48.0	+55.15	48.43	77.67	-29.24	14.37	15.9	-1.53	Pitressin
2d.	43.40	19.6	+23.80	110.84	45.4	+65.44	41.42	70.0	-28.58	14.48	14.9	- .42	
Mean:	43.50	31.96	+11.54	110.34	59.18	+51.16	43.35	73.74	-30.39	14.46	15.25	- .79	

N.B. Washed red blood cells contain 94 meq./litre potassium.

Calculated dietary potassium for one day 87.4 meq.
Actual potassium content of same diet 84.2 meq.

Potassium content of feces approximately 90 meq. per day.

Thermo-sweat contains 49 meq./l of potassium.

N.B. All values shown are average daily values for each daily period.

TABLE VII (A)

URINARY BALANCE DATA

Showing the effects of cortisone.

Mr. M.A. #81123
Epilepsy III

		SODIUM (Meq.)			POTASSIUM (Meq.)			CHLORIDES (Meq.)			NITROGEN (Kms.)			
PERIOD NUMBER	NUMBER OF DAYS	IN	OUT	BAL.	IN	OUT	BAL.	IN	OUT	BAL.	IN	OUT	BAL.	TREATMENT
1	2	43.69	119.56	-75.8	101.25	60.5	+40.75	42.31	79.25	-36.94	14.26	13.5	+ .76	Control
2	2	43.57	43.04	+ .53	109.86	81.5	+28.36	43.22	38.5	+ 4.72	14.45	16.0	-1.55	Control
3	3	43.45	30.4	+13.05	102.02	87.2	+14.82	46.42	55.5	-9.08	14.41	16.36	-1.95	Cortisone
4	3	43.49	21.3	+22.19	111.71	69.7	+41.97	42.64	18.63	+24.01	14.49	16.5	-2.01	Cortisone
5	4	43.46	42.72	+ .74	110.49	86.0	+24.47	45.99	33.28	+12.71	14.29	16.8	-2.51	Cortisone
6	3	43.47	20.29	+23.18	109.49	72.4	+37.01	38.76	23.04	+15.72	14.47	17.4	-2.93	Cortisone
7	3	43.17	27.03	+16.14	102.31	68.5	+33.8	42.19	23.2	+18.99	14.61	17.5	-2.89	Cortisone
8	3	43.48	89.53	-46.05	110.61	78.5	+32.08	40.52	58.86	-18.34	14.33	15.9	-1,57	Control
9	3	43.47	42.3	+ 1.17	98.88	86.8	+12.11	44.86	37.95	+ 6.91	14.41	15.7	-1.29	Control

TABLE VII B

BIOCHEMICAL DATA

		SERUM						URINE					
PERIOD NUMBER	Na Meq./l	K Meq./l	Cl Meq./l	CO_2 Meq./l	Eosin	17-KS.	Cortin	Creat-	Volume Urine	Sp. Gr.	B.P.	Kgm. Weight	TREATMENT
1	124	4.4	109.9	21.3	55	6.85	1.11	1.41	1855	1.012	140/93	55.7	Control
2	124	4.6	109.0	25.9	99	6.92	.58	1.39	1505	1.012	137/101	55.9	Control
3					22	7.79	1.51	1.36	1623	1.012	129/92	55.7	Cortisone
4	125	3.98	108.0	29.1	0	10.35	2.54	1.56	1090	1.017	132/93	55.0	Cortisone
5	130	4.18	104.6	29.8	20	23.5	2.54	1.40	1498	1.014	132/88	55.8	Cortisone
6	132	4.54	93.2	25.5	0	19.9	2.45	1.55	1037	1.020	133/91	55.7	Cortisone
7	127	3.96	106.4	27.7	11	19.75	2.61	1.51	1353	1.015	138/92	56.0	Cortisone
8	127.5	4.05	106.4	27.1	60	8.60	1.11	1.51	1722	1.012	127/89	55.6	Control
9	127.5	4.5	107.2	25.9	88	6.51	1.01	1.51	1480	1.013	123/89	54.7	Control
Mean				26.5				1.49	1463	1.014	133/92	55.6	
Sp. Dev.				±2.5				±.05	±232	±.003		±.4	

TABLE VIII A
URINARY BALANCE DATA

Chronic Rheumatoid Arthritis
Mr. F. #27645

SHOWING EFFECTS OF DILANTIN AND MESANTOIN

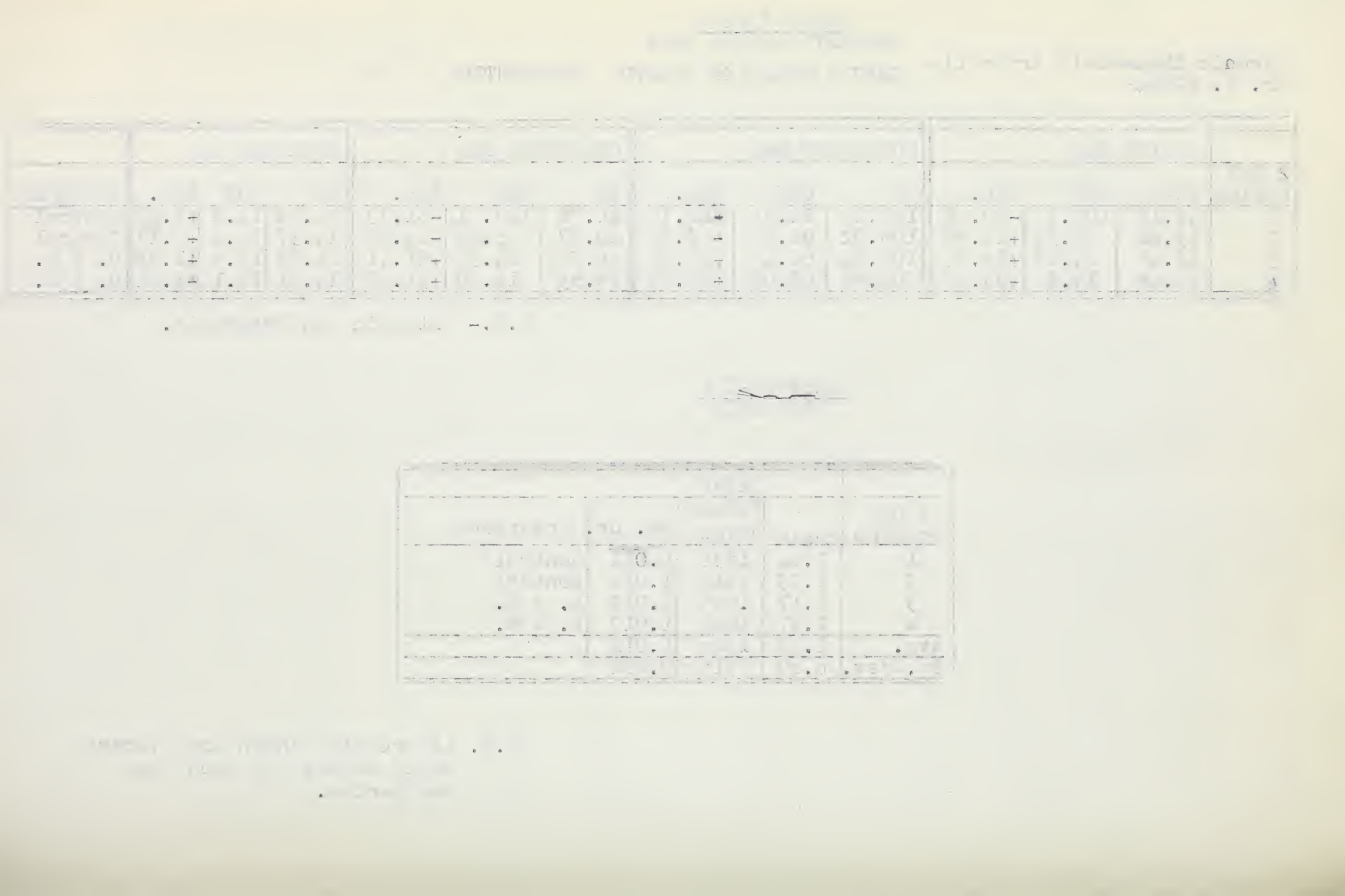
2 DAY PERIOD	SODIUM Meq			POTASSIUM Meq			CHLORIDES Meq			NITROGEN Meq			
	IN	OUT	BAL.	IN	OUT	BAL.	IN	OUT	BAL.	IN	OUT	BAL.	TREATMENT
1	44.12	104.2	-60.08	122.15	81.85	+40.30	41.78	103.51	-61.73	14.38	11.8	+2.58	Control
2	43.48	28.89	+14.59	105.02	96.3	+ 8.72	40.77	55.43	-14.66	14.37	14.2	+0.17	Control
3	43.46	24.62	+18.84	102.04	64.4	+37.64	45.75	24.34	+21.41	14.38	12.5	+1.88	D. & M.
4	43.46	19.8	+23.66	96.83	68.08	+28.75	45.65	14.29	+31.36	14.31	11.1	+3.21	D. & M.

N.B.- Dilantin and Mesantoin.

TABLE VIII B
URINE DATA

2 DAY PERIOD	URINE			
	Creat.	Volume Urine	Sp. Gr.	Treatment
1	1.14	1835	1.011	Control
2	1.25	1410	1.014	Control
3	1.17	1095	1.015	D. & M.
4	1.37	1045	1.017	D. & M.
Avg.	1.23	1346	1.014	
St. dev.	±0.09	± 315	±0.002	

N.B. All results shown are average daily values for each two day period.



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